National Institute of Allergy and Infectious Diseases

PROFILE

Fiscal Year 2002

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

National Institute of Allergy and Infectious Diseases

PROFILE

Fiscal Year 2002

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) supports and conducts basic and applied research to better understand, treat, and prevent infectious, immunologic, and allergic diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as: bioterrorism; emerging and re-emerging infectious diseases, including Acquired Immunodeficiency Syndrome (AIDS), West Nile virus, dengue, malaria, and tuberculosis; and the increase in asthma among children in this country. The growth of NIAID programs also has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology, immunology, and infectious diseases. Advances in these key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

The final four months of 2001 were among the most extraordinary—and tragic—in American history. The September 11 attacks on the World Trade Center and the Pentagon have transformed our society in many ways. Superimposed on this tragedy were the first known cases of anthrax in the United States to result from an intentional human act. These two events mobilized a new effort to bolster what has come to be known as Homeland Security, a multifaceted endeavor that includes, among many other components, defenses against and responses to bioterrorism.

Our nation's ability to detect and counter bioterrorism depends to a large degree on the state of biomedical science. As the lead agency at NIH for infectious diseases and immunology research, NIAID has developed the *NIAID Strategic Plan for Biodefense Research* and the detailed *NIAID Biodefense Research Agenda for CDC Category A Agents*, with short-, intermediate-, and long-term goals. The Strategic Plan and Research Agenda stress two overarching and complementary components: **basic research** into agents with bioterrorism potential and the specific and nonspecific host defense mechanisms against those agents, and **applied research** with predetermined milestones for the development of new or improved diagnostics, vaccines, and therapies.

We anticipate that the large investment in research on biodefense will have many positive spin-offs for other diseases. The planned NIAID research on microbial biology and on the pathogenesis of organisms with bioterror potential will certainly lead to an enhanced understanding of other more common and naturally occurring infectious diseases that afflict people here and abroad. In particular, the advancement of knowledge should have enormous positive impact on our ability to diagnose, treat, and prevent major killer-diseases such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and re-emerging diseases, such as West Nile virus, dengue and influenza, as well as multi-drug-resistant microbes. Furthermore, and importantly, the NIAID biodefense research agenda promises to enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system. Such knowledge will help in the search for new ways to treat and prevent a variety of immune-

mediated diseases, such as systemic lupus erythematosus, type 1 diabetes, and rheumatoid arthritis. New insights into the mechanisms of regulation of the human immune system will also have positive spinoffs for diseases such as cancer, immune-mediated neurological diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of transplanted organs, cells, and tissues.

Vaccine research, so important to our preparedness against future bioterrorism attacks, has long been a cornerstone of NIAID research. NIAID-supported investigators helped develop many new and improved vaccines that are now used widely; these vaccines have saved literally millions of lives and prevented untold illness and disability from infectious diseases. Success stories include the development of vaccines against *Haemophilus influenzae* type b, pertussis, chickenpox, pneumococcal disease, and hepatitis A and B. NIAID has three broad goals in vaccine research: identifying new vaccine candidates to prevent diseases for which no vaccines currently exist; improving the safety and efficacy of existing vaccines; and designing novel vaccine approaches, such as new vectors and adjuvants. To speed these efforts, NIAID has made a significant investment in the growing field of microbial genomics and, in FY 2002, supported approximately 50 large scale projects for sequencing the genomes of microbial pathogens and invertebrate vectors of infectious diseases. Approximately 30 of these projects have been completed, including the genomic sequences of bacteria that cause tuberculosis, gonorrhea, chlamydia, and cholera; the parasite that causes malaria; and the mosquito that transmits malaria. The availability of the genomic sequences of these and other organisms will facilitate the identification of a wide array of new antigens for vaccine targets.

One of the important challenges for the 21st century is the development of safe and effective vaccines for the three greatest microbial killers worldwide: HIV/AIDS, malaria, and tuberculosis. These three diseases account for one-third to one-half of healthy years lost in less developed countries. NIAID has a robust portfolio of vaccine research and development for these and other diseases of global importance.

Despite recent progress in treatment and prevention, human immunodeficiency virus (HIV) disease and AIDS continue to exact an enormous toll throughout the world. More than 40 million people are living with HIV/AIDS, and another 25 million people with HIV/AIDS have died. More than 95 percent of these infections and deaths have occurred in developing countries, most of which are also burdened by other significant health challenges.[1] In these nations, HIV/AIDS threatens not only human welfare but also social, political, and economic stability. In the United States, an estimated 950,000 people are living with HIV/AIDS; approximately 470,000 deaths among people with AIDS were reported to the Centers for Disease Control and Prevention by the end of 2001.[2]

In the United States and other western countries, potent combinations of anti-HIV drugs (highly active antiretroviral therapy, or "HAART") have dramatically reduced the numbers of new AIDS cases and AIDS deaths. However, the toll of AIDS has accelerated elsewhere in the world, especially in poor countries where expensive HAART regimens

are beyond the reach of all but a privileged few. Fortunately, this disparity in access to life-saving medications may be changing. Building on the research infrastructure that NIAID has helped establish in Africa and elsewhere in the developing world, we are actively working with our international colleagues to link the provision of anti-HIV therapy to efforts in prevention research, with the goal of facilitating a comprehensive approach to the AIDS pandemic in poor countries. Concurrently, NIAID-supported investigators are testing diverse HIV prevention and vaccine strategies. Prevention efforts in our country and abroad focus on several key areas, including behavioral modification, interventions to prevent mother-to-infant transmission of HIV, and the development of topically applied microbicides that women could use to protect themselves against HIV and other sexually transmitted pathogens. Several vaccine candidates have recently shown remarkable promise in nonhuman primates. The best candidates are rapidly being moved into human clinical trials at sites of NIAID's HIV Vaccine Trials Network in the United States and abroad, and at the NIAID Vaccine Research Center.

NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals with immunologic conditions such as multiple sclerosis, type 1 diabetes, and asthma. Researchers are developing novel ways of selectively blocking inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as tolerance induction. The NIAID-supported Immune Tolerance Network (ITN) is an international consortium consisting of approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. To date, the ITN has 18 approved clinical protocols that are enrolling patients, or will do so soon, in areas such as islet transplantation for type 1 diabetes, kidney transplantation, autoimmune diseases, and asthma and allergic diseases.

For the past decade, NIAID also has focused on reducing the significant and growing burden of asthma among inner-city minority children. NIAID's Inner-City Asthma Study has investigated novel interventions to improve the health of inner-city children with asthma. One approach, called a physician feedback intervention, involves periodic reports to the child's doctor about the status of the child's asthma. These reports, generated from bimonthly phone interviews with parents, recommend changes in the child's treatment regimen according to National Heart, Lung, and Blood Institute (NHLBI) guidelines, if warranted. Another method involves an environmental intervention to identify and remove asthma triggers, such as cigarette smoke or cockroaches, from the child's home. Both interventions are reducing health care utilization, and the children receiving the environmental intervention gained an additional 3 weeks of symptom-free days during the intervention year. We are working to make such interventions available nationwide.

Profile describes the Institute's activities in areas of basic research and clinical investigation and provides overviews of the major accomplishments and goals of the various scientific programs within the Institute. *Profile* also includes information on the organization and staff of NIAID, the Institute's budget, and its extramural grants, contracts, and research training programs.

With a strong research base, talented investigators in the United States and abroad, and the availability of powerful new research tools, we fully expect that our basic and applied research programs will provide the essential elements to enhance our defenses against those who would attempt to harm us with bioterrorism, to develop new tools in the fights against HIV/AIDS and other infectious diseases, and to improve therapies and management of immune-mediated diseases.

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases

[1] UNAIDS. Report on the Global HIV/AIDS Epidemic, 2002: "The Barcelona Report."

[2] Fleming, PL et al. HIV Prevalence in the United States, 2000. Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, Feb. 24-28, 2002. Abstract 11.

TABLE OF CONTENTS

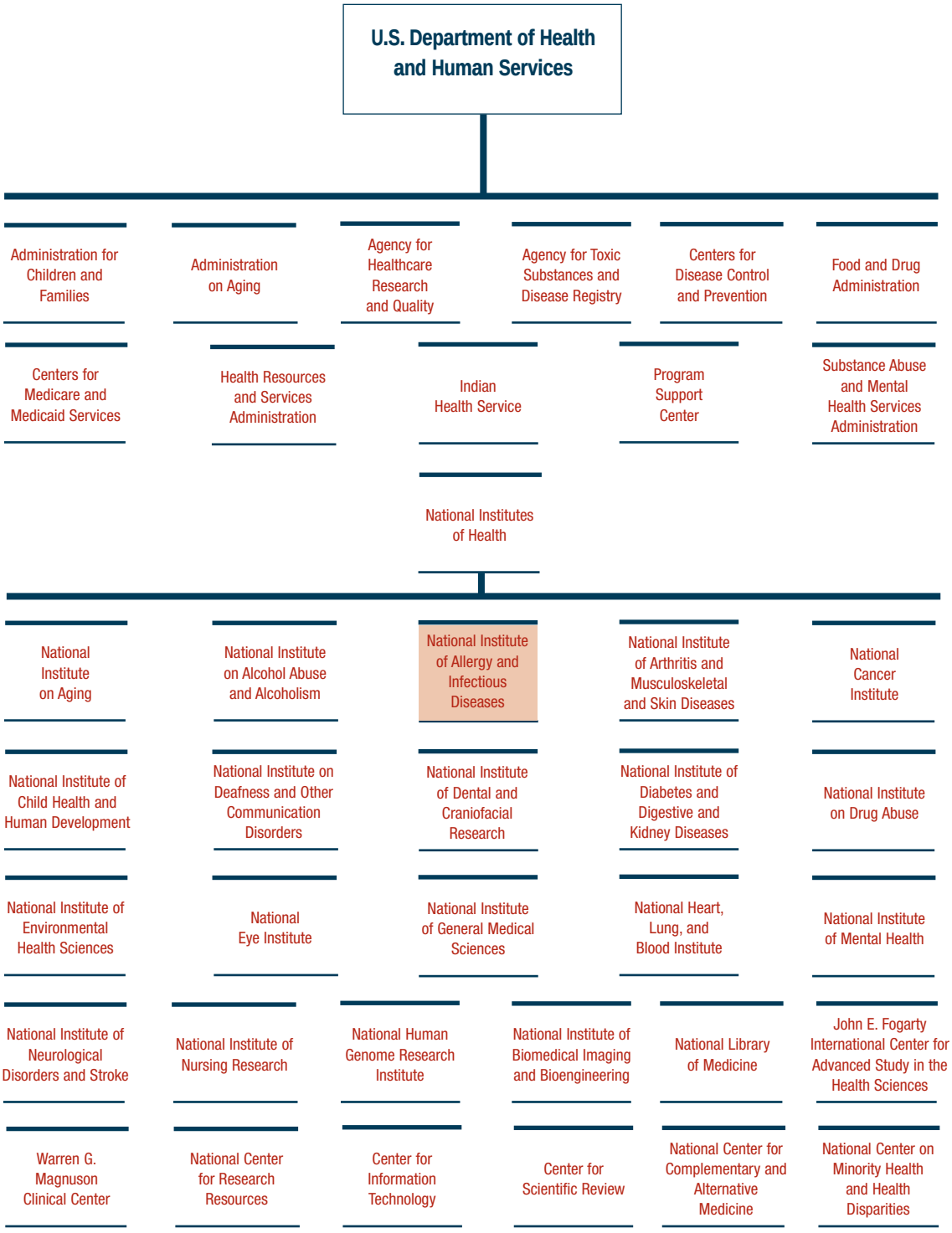
Council, Review Committees, and Working Group

Budget Overview and Historical Trends

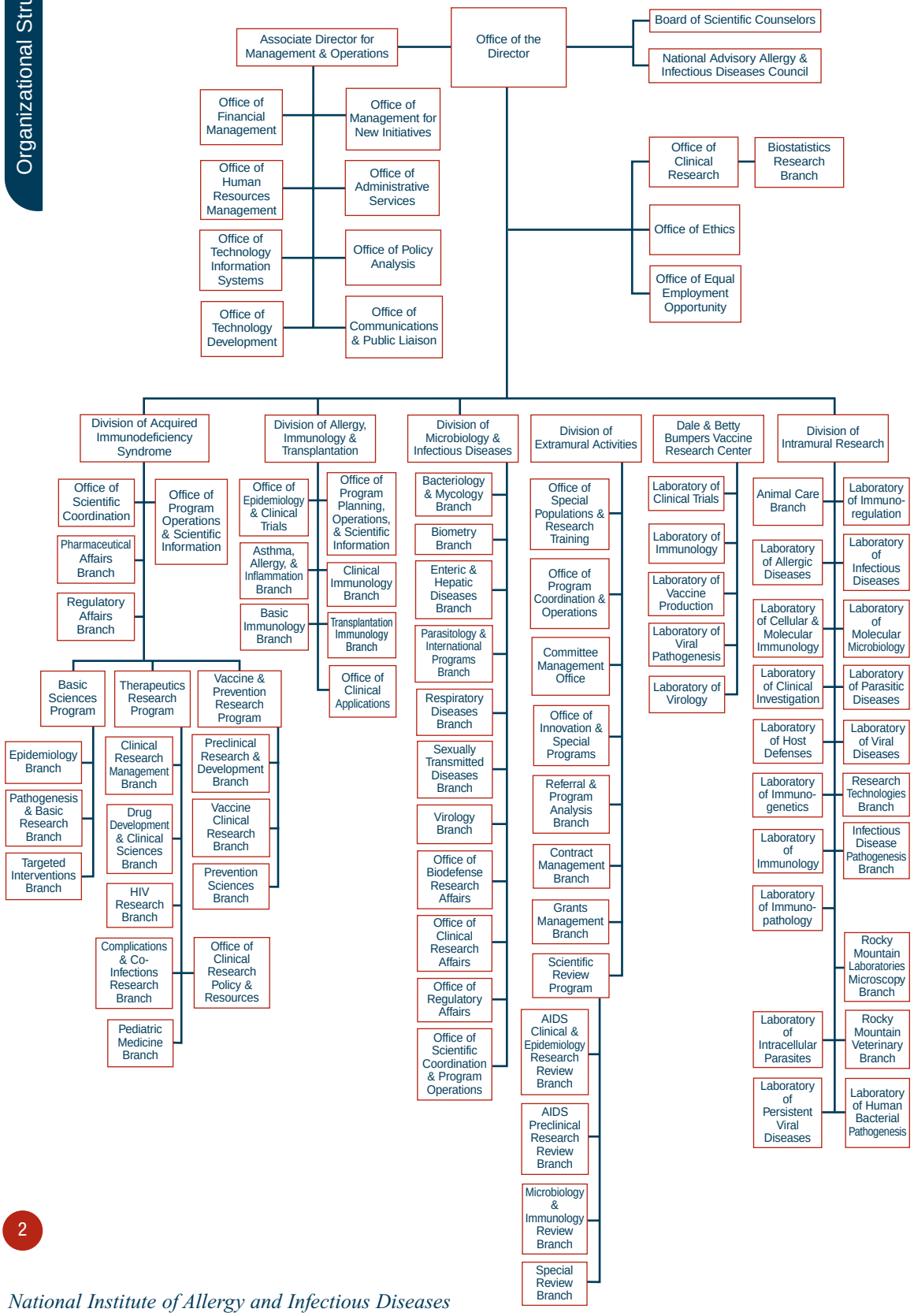
Appendices

General Information

Location of NIAID in the U.S. Department of Health and Human Services



NIAID Organizational Chart



NIAID DIRECTOR

Anthony S. Fauci, M.D., became the Director of NIAID in 1984. As NIAID Director, he oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma, and allergies. He also serves as one of the key advisors helping guide Department of Health and Human Services initiatives to bolster medical and public health preparedness against possible bioterrorist attacks.

Dr. Fauci was born in Brooklyn, New York, and received his undergraduate degree from Holy Cross College in 1962 and his medical degree from Cornell University Medical College in 1966. He completed his internship and residency at The New York Hospital-Cornell Medical Center and joined NIAID in 1968 as a clinical associate in the Laboratory of Clinical Investigation. In 1980, Dr. Fauci became Chief of the NIAID Laboratory of Immunoregulation, a post he continues to hold.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He is an internationally renowned scientist and has pioneered the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. In addition, Dr. Fauci is widely recognized for delineating the precise mechanisms whereby immunosuppressive agents modulate the human immune response. He has developed effective therapies for formerly fatal diseases such as polyarteritis nodosa, Wegener's granulomatosis, and lymphomatoid granulomatosis.

Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses, leading to its susceptibility to deadly infections. He also has delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease, as well as for a vaccine to prevent HIV infection. He continues to devote much of his research time to identifying the nature of the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to the AIDS retrovirus.

During his career as a biomedical researcher, Dr. Fauci has authored, coauthored, or edited more than 1,000 scientific publications. He has served as a visiting professor at medical centers throughout the country and has delivered many major lectures at institutions and conferences all over the world.

Dr. Fauci is a member of the prestigious National Academy of Sciences, the American Philosophical Society, the Royal Danish Academy of Science and Letters, the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences, where he is a Council member. He also is a member of many professional organizations, including the American College

of Physicians, the Infectious Diseases Society of America, the American Society for Clinical Investigation, the Association of American Physicians, and the American Academy of Allergy, Asthma and Immunology. Dr. Fauci serves on a number of editorial boards and is an editor of *Harrison's Principles of Internal Medicine.* He has received numerous awards for his scientific accomplishments, including 24 honorary doctorate degrees.

OFFICE OF THE DIRECTOR

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. The OD is the focal point of relationships with the Director of the National Institute of Health, as well as with other components of the Department of Health and Human Services, other Federal agencies, Congress, professional societies, voluntary health organizations, and other public groups. The activities of the OD also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs.

Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, the OD offices play a key role in helping the Institute achieve its mission. Brief descriptions of the OD offices follow.

The Office of Administrative Services (OAS) assists NIAID staff in carrying out their responsibilities by providing administrative and acquisition management support services. These services include procurement, space management, and travel. OAS also develops internal controls in areas such as property accountability and financial monitoring, and coordinates and analyzes organizational changes.

The Office of Clinical Research manages and coordinates those NIAID research programs conducted at the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board to provide initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office also provides relevant information from NIAID's intramural clinical research programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Communications and Public Liaison (OCPL) enables NIAID to meet an important part of its mission by conveying the goals and results of its research programs to health professionals, the news media, and the public. In addition to responding to more than 10,000 requests for information annually, the Office: plans educational and media campaigns; develops and disseminates brochures, fact sheets, news releases, and audiovisual products; and produces educational exhibits for national and regional meetings. OCPL also coordinates NIAID's Web site activities.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and persons with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities to implement NIH minority-assistance programs and objectives relevant to the mission of NIAID.

The Office of Ethics provides advice regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee

members, and non-Government employees such as peer reviewers and Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

The Office of Financial Management, provides overall financial planning, management and budget analysis to the Institute Director and all NIAID components, as well as budget-related materials for the NIAID Director's briefings with the Department of Health and Human Services, the NIH Director, the Office of Management and Budget, and Congress.

The Human Resources Operations Branch C (NIAID), Division of Human Resources Operations, Office of Human Resources, NIH, provides human resource services for the Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, employee benefits, employee development, and advisory services.

The Office of Management for New Initiatives (OMNI) is responsible for managing the establishment of key resources for new NIAID scientific and administrative initiatives. This office also is charged with acquiring and developing physical, human, and contractual infrastructure to fulfill new and expanded NIAID mission requirements.

The Office of Policy Analysis (OPA) provides support and serves as liaison to program managers to: coordinate, integrate, and articulate long-range program goals and strategies; develop and coordinate the Institute's annual planning and reporting process; advise on material for all stages related to congressional budget presentations; direct and coordinate the legislative liaison, tracking, and analysis for the Institute; manage the Executive Secretariat function; direct and coordinate Freedom of Information Act (FOIA) activities; provide the secretariat function for selected advisory groups, such as the NIAID Executive Committee; prepare the Institute Director for meetings with various constituency groups; and brief the NIAID Director in preparation for trans-NIH policy meetings.

The Office of Technology Development (OTD) supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff uses scientific, legal, and business expertise to negotiate agreements with universities, small biotechnology companies, large national and multinational pharmaceutical concerns, and other government institutions. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD also manages the receipt of Cooperative Research and Development Agreement (CRADA) funds, supports NIH's licensing program, and tracks license royalty receipts. In addition, OTD provides NIAID investigators with training on NIH technology transfer policies and regulations and guidance on conflict of interest issues.

The Office of Technology Information Systems (OTIS) manages local and wide area network support for NIAID. The Office also develops applications software and provides application support for NIAID computer databases, and provides training, professional development, and consultative services. In

addition, OTIS provides information technology to support NIAID's mission of sponsoring and conducting medical research, and supplies NIAID's intramural and extramural scientific communities and administrative staffs with the capability to readily access, process, and disseminate scientific and administrative information to Congress, the Administration, Federal agencies, other nations, and the public.

OUTREACH ACTIVITIES

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for disseminating research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops and conferences for community health care providers and the public.

OCPL produces materials on topics ranging from allergic and immunologic diseases, to AIDS and other sexually transmitted diseases, to potential illnesses caused by agents of bioterrorism. These materials include press releases, information sheets, and booklets, which are distributed to more than 10,000 people who contact the Institute from around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID Web site (*www.niaid.nih.gov*), which is now visited 1.5 million times each month.

The NIAID Web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. The Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

OCPL reprinted its very popular low-literacy booklets on tuberculosis (TB)—*Tuberculosis and Tuberculosis Infection.* Both are available in Spanish. OCPL staff also updated and printed the booklet titled *Malaria*. Malaria, like TB and HIV/AIDS, is a serious disease that kills millions of people worldwide. OCPL distributed thousands of copies of the previous edition to researchers and health care providers around the world. All publications also are available on the NIAID Web site.

A new OCPL communications initiative expands NIAID's efforts to keep more than 400 voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of the organizations. In addition, OCPL disseminates news from the NIH Offices of Public Liaison, which include NIAID.

Exhibiting at scientific and health-related meetings is a key element of OCPL's outreach efforts. Institute staff distribute materials and answer questions about NIAID research and job opportunities at conferences, including the American Academy of Allergy, Asthma and Immunology; the American Society for Microbiology; the National Conference on Blacks in Higher Education; the Hispanic Association of Colleges and Universities; the American Public Health Association; and the Congressional Black Caucus. OCPL has been involved extensively in the outreach efforts of NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC). The VRC is the first facility at NIH dedicated solely to vaccine research and production. As the center prepares for its second HIV vaccine trial, OCPL is helping to construct community partnerships by targeting local news media, visiting local churches and other community organizations, and attending HIV/AIDS-related conferences and meetings.

The NIAID Division of AIDS (DAIDS) is conducting a national HIV vaccine communications campaign to foster a better public awareness of HIV vaccine research. The

campaign is designed to create a public dialogue to help the public better understand the research, support it, and support those who may volunteer for clinical trials. The Institute implemented a qualitative comprehensive research effort, including both primary research (for example, 28 focus groups representing communities most affected by HIV/AIDS) and secondary, or existing, research. Staff used the findings to plan and target the campaign strategy and message development.

A key component for the first year of the campaign was to engage "early adopters," those individuals and organizations that represent target audiences and are currently involved in HIV/AIDS prevention and treatment efforts.

Roundtable discussions were held with leaders in the African-American and Latino communities to refine strategies and to engage participants in ongoing activities, such as materials development and outreach.

In coordination with NIAID's HIV Vaccine Trials Network, DAIDS implemented an advertising campaign targeting opinion leaders, especially in communities most affected by HIV/AIDS, and substantial print and broadcast outreach that publicly reveal key messages about HIV vaccine research. Workshops on HIV vaccine research were featured at scientific conferences, including AIDS Vaccine 2002 and the Conference on Retroviruses and Opportunistic Infections.

RESEARCH PLANNING

NIAID has a long-standing tradition of rigorous and prospective research planning, involving the development and prioritization of specific research initiatives on an annual basis and long-range, strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report titled *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health.* The two pillars of this research planning process are the annual Summer Program Review (SPR) and the Winter Policy Retreat (WPR).

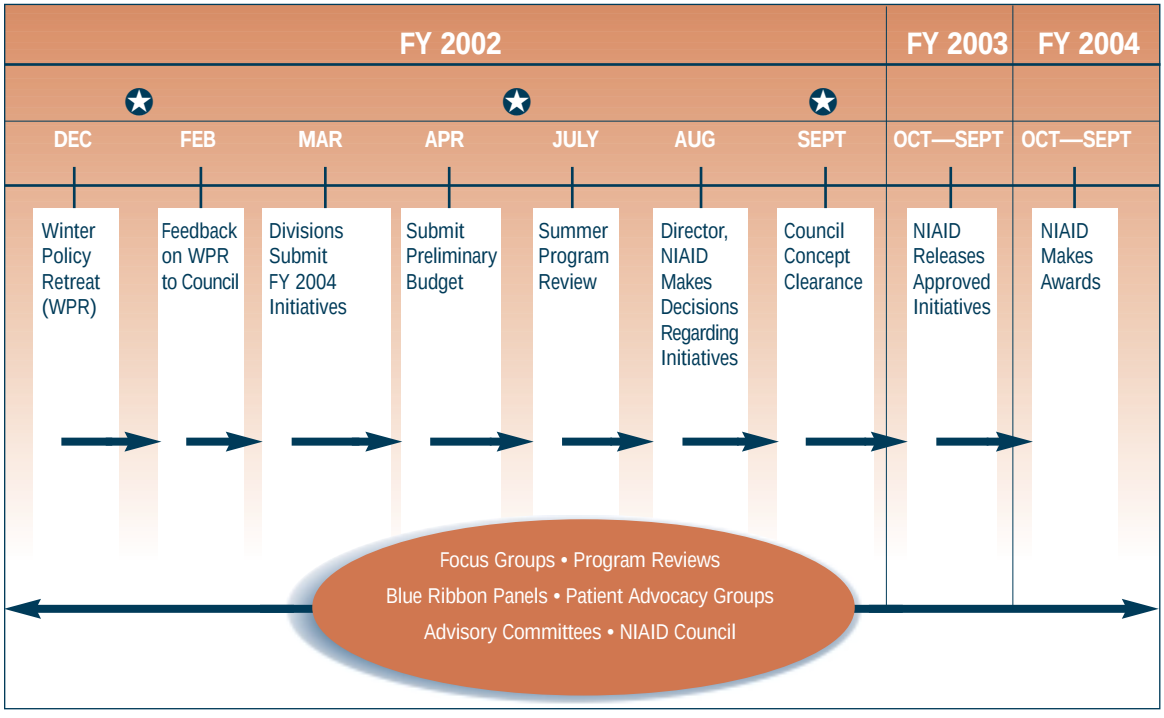
Program Reviews

NIAID's annual program reviews are designed to develop and select future initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews are to:

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify the basis for scientific opportunities and gaps;
- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose approaches for responding to newly identified opportunities and needs;
- Identify the implications of changes in scientific or programmatic direction; and
- Prioritize newly identified opportunities and needs within the future budget year.

NIAID PRIORITY SETTING PROCESS



= Council Meetings

Policy Retreats

The planning process is further enriched through annual policy retreats to:

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Use this information to make decisions about research activities and initiatives to be implemented in the future budget year.

Throughout the year, NIAID convenes scientific workshops, blue ribbon panels, and program reviews to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, including scientific experts, professional societies, and patient advocacy groups, to develop long-range, strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by the Department of Health and Human Services, the NIH, Congress, the White House, and others, also help shape the Institute's decision making and priority setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins two years in advance of the projected implementation date. At each step in the process, the concepts for research initiatives are reviewed and refined. Concepts are first subjected to internal discussion during the annual program review, followed by a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council (NAAIDC). Approved concepts are then developed by NIAID staff into various forms of grant and contract solicitations and announced to the scientific community. Proposed research projects are then peer reviewed and awarded on the basis of scientific merit, program relevance, and need.

Strategic Planning

NIAID's comprehensive strategic plan, *NIAID: Planning for the 21st Century*, is the product of an intensive effort that included a task force of national experts. The plan describes broad-based priorities to guide NIAID programs, policies, and initiatives through the next three to five years. The cornerstones of the plan are: (1) immune-mediated diseases; (2) human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); (3) emerging infectious diseases and global health; and (4) vaccines. The full text of the plan can be accessed at *http://www.niaid.nih.gov/strategicplan.*

The Institute's guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis.* This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at *http://www.niaid.nih.gov/publications/globalhealth/global.pdf.*

In FY 2002, NIAID convened four expert panels to assist in the development of strategic plans and research agendas that address critical needs.

- *The NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research* assisted in developing the *NIAID Strategic Plan for Biodefense Research* and the *NIAID Biodefense Research Agenda for CDC Category A Agents.* The Strategic Plan emphasizes basic research on microbes, host defense mechanisms, and the development of drugs, vaccines, and diagnostics. The Biodefense Research Agenda articulates immediate and longer-term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus. The agenda also addresses the research resources, facilities, and scientific manpower needed to conduct basic and applied research on these potential agents of bioterrorism. Both the Strategic Plan and the Research Agenda can be accessed at *http://www.niaid.nih.gov/publications/bioterrorism.htm.*

- The *NIAID Expert Panel on Atopic Dermatitis and Vaccinia Immunization* focused on the morbidity and mortality associated with administering existing smallpox vaccines to persons with eczema and other skin conditions.

- The *NIAID Expert Panel on Immunity and Biodefense* addressed the immunological aspects of biodefense research, including innate and adaptive immune responses. A summary of this expert panel meeting can be accessed at *http://www.niaid.nih.gov/publications/bioterrorism.htm*

- The *NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research on Category B and C Agents* assessed current research initiatives and goals for a diverse range of pathogens, including those that cause cholera, typhus fever, and yellow fever, as well as toxins that are secreted by certain microbes. A summary of this meeting can be accessed at *http://www.niaid.nih.gov/publications/bioterrorism.htm.*

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The *NIAID Strategic Plan for Addressing Health Disparities* articulates specific action plans for reducing disparities through: (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at *http://www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.*

DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) (*www.niaid.nih.gov/daids*) was formed in 1986 to develop and implement the national research agenda to address the HIV/AIDS epidemic. Today, with the ever-changing demographics of the epidemic, DAIDS is expanding its focus to a more global research agenda with an emphasis on an integrated prevention and therapeutics agenda in developing nations. Specifically, the mission of DAIDS is to help ensure an end to the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus, or HIV; supporting the development of therapies for HIV infection and its complications; and supporting the development of vaccines and other prevention strategies. DAIDS accomplishes its mission through planning, implementing, managing, and evaluating programs in (1) fundamental basic research, (2) discovery and development of therapies and treatment strategies for HIV infection and its complications, and (3) discovery and development of vaccines, topical microbicides, and other prevention strategies. To achieve its mission, DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. By surveying developments in key research areas, DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with advisory groups and community and health professional organizations, evaluating and redirecting program emphasis to respond to changing global research needs.

Scientific Areas of Focus

Basic Research

Basic research continues to increase our understanding of the biology of HIV and how the immune system responds to the virus. Knowledge gained from these studies enhances the ability of researchers to create new therapeutic agents and vaccines to combat HIV infection. DAIDS supports a large portfolio of investigator-initiated grants in HIV pathogenesis and epidemiology that are pursuing research in a variety of areas, including mechanisms of viral entry and infection; the structure, function, and mechanism of action of viral genes and proteins; the roles of cellular accessory molecules in replication; the immunologic and virologic events controlling primary infection and formation of the latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified new structures for viral components of HIV, how HIV uses the host machinery to exit the cell, and the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication and about why the host immune response is not fully effective in controlling the infection. Information about

how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

The Division's therapeutics research program supports the discovery and development of effective therapies for HIV/AIDS and associated opportunistic infections (OIs) by facilitating and expediting research on highly promising candidate agents and novel therapeutic concepts. Through strategic planning and funding, DAIDS supports research on potential new cellular and viral therapeutic targets, enhanced formulations of existing agents, and treatment regimens to improve adherence, minimize toxicities, and impede emergence of resistance. In addition, the Division supports research on approaches to restore the immune system, to protect uninfected cells, and to improve assays to measure pathogen load and host immunity. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans. The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. These clinical studies define new agents that are effective against HIV and its associated OIs and clarify how best to use these drugs. Human testing of anti-HIV therapeutics is carried out in three large DAIDS-sponsored clinical trials networks: the Adult AIDS Clinical Trials Group (AACTG) (*http://aactg.s-3.com*), the Pediatric AIDS Clinical Trials Group (PACTG) (*http://pactg.s-3.com*), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) (*www.cpcra.org*). In addition, research on acute HIV infection is conducted through the Acute HIV Infection and Early Disease Research Program (AIEDRP) (*http://aiedrp.fhcrc.org*).

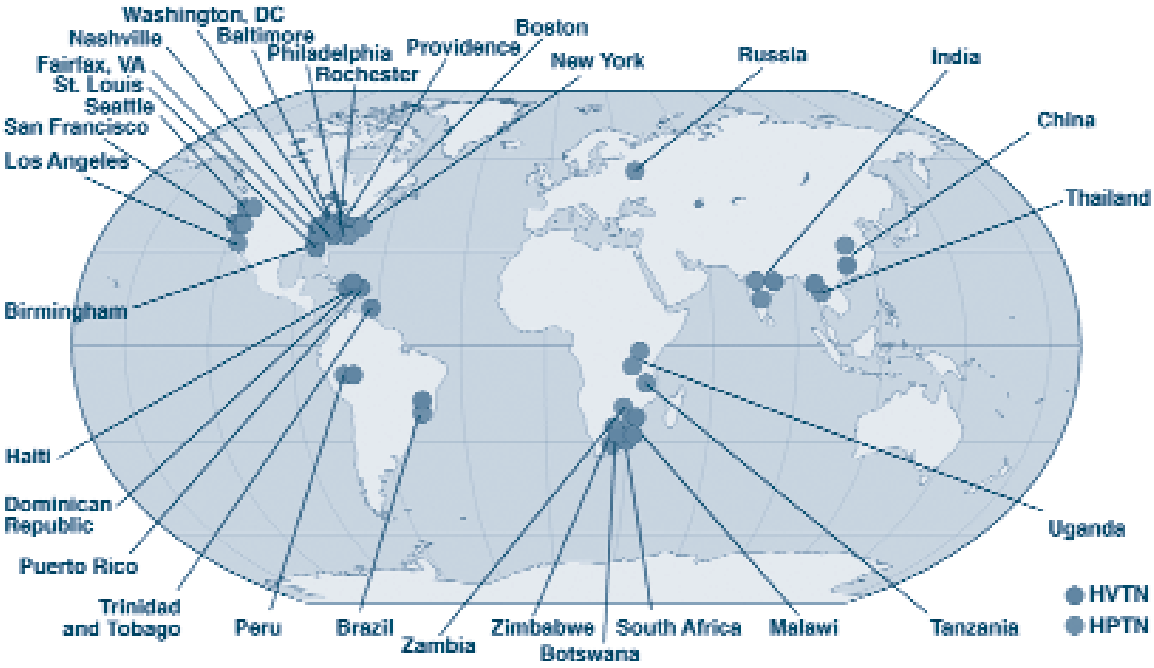
DAIDS-sponsored therapeutics research already has had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define national and international guidelines for the treatment of primary HIV infection and associated OIs as well as prophylactic regimens for these secondary infections; (2) identified biological markers, such as CD4+ counts, and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and ways to rebuild and replace immunity lost to HIV infection. In addition, the Division is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy and the optimal approach to medical management.

Vaccine and Prevention Research

The development of safe and effective vaccine and nonvaccine strategies for the prevention of

NIAID HIV VACCINE AND PREVENTION TRIALS NETWORKS (HVTN AND HPTN) DOMESTIC AND INTERNATIONAL SITES



HIV infection and AIDS is a high priority of NIAID. DAIDS supports all phases of the discovery and development of preventive HIV vaccines, including basic research, preclinical testing, and human clinical testing of candidate HIV vaccines. Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (*www.hvtn.org*). The HVTN, which was formed in 2000, is a global network designed to develop and conduct a comprehensive HIV vaccine clinical research agenda that addresses the scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. The HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. (Additional information on the HVTN is located in the Vaccine Research and Development section of Selected Scientific Areas of Research on page 129).

DAIDS also supports research on other biomedical and behavioral approaches to preventing the spread of HIV/AIDS. These approaches include drugs or vaccines that prevent MTCT of HIV, microbicides for preventing sexual transmission of HIV, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted diseases, and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners. NIAID-supported prevention clinical trials are centered in the HIV Prevention Trials Network (HPTN) (*www.hptn.org*). The HPTN, also formed in 2000, is a global, multicenter network dedicated

to prevention research with a focus on HIV end points. The HPTN is supported by the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse. (Additional information on the HPTN is located in the AIDS section of Selected Scientific Areas of Interest on page 45.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, further explained the envelope structure of HIV, advanced our understanding of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes (CTLs), developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies must address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. With regard to other prevention research, new microbicides must be developed and tested to prevent the sexual transmission of HIV. In addition, to build on its past success in identifying an inexpensive regimen that reduces HIV transmission at birth, the Division must develop new, more effective regimens for preventing MTCT of HIV, especially during breastfeeding. These regimens must be practical for use in developing countries.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. These research programs are designed to advance global research priorities; ensure the clinical relevance of future vaccine, prevention, and treatment strategies to human populations most in need; strengthen collaborations with local investigators worldwide; and support training and infrastructure development in developing countries.

Major Programs and Networks

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- Comprehensive International Program of Research on AIDS
- HIV Prevention Trials Network
- HIV Therapeutics: Targeting Research Gaps
- HIV Vaccine Design and Development Teams Program
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Research and Design Program
- HIV Vaccine Trials Network
- Innovation Grants for AIDS Research Program

- Integrated Preclinical/Clinical Program for HIV Topical Microbicides
- Integrated Preclinical/Clinical Vaccine Development Program
- Laboratory Methods to Assess Responses to HIV Vaccine Candidates
- Liver and Pancreatic Disease in HIV Infection Program
- Multicenter AIDS Cohort Study
- National Cooperative Drug Discovery Groups—Opportunistic Infections
- New Technologies for HIV and HIV Vaccine-Related Research Program
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program
- Women and Infants Transmission Study
- Women's Interagency HIV Study

NIAID HIV Vaccine and Prevention Trials Networks

(HVTN and HPTN) Domestic and International Sites

The **HVTN** domestic and international clinical sites and their principal investigators are as follows:

United States

Alabama

- University of Alabama at Birmingham—Mark Mulligan, M.D.

California

- San Francisco Department of Health, San Francisco—Susan Buchbinder, M.D.
- Mount Zion Hospital, San Francisco—Susan Buchbinder, M.D.

Maryland

- University of Maryland, Baltimore—William Blattner, M.D.
- Johns Hopkins University, Baltimore—Donald Burke, M.D.

Massachusetts

- Fenway Community Health, Boston—Kenneth Mayer, M.D.
- Harvard University—Brigham and Women's Hospital, Boston—Raphael Dolin, M.D., and Lindsay Baden, M.D.

Missouri

- Saint Louis University—Robert Belshe, M.D.

New York

- Columbia University, New York—Scott Hammer, M.D.
- New York Blood Center–Union Square—Beryl Koblin, Ph.D.
- New York Blood Center–Bronx—Beryl Koblin, Ph.D.
- University of Rochester, Rochester—Michael Keefer, M.D.

Puerto Rico

- Universidad de Puerto Rico, San Juan—Carmen Zorrilla, M.D.

Rhode Island

- Miriam Hospital, Providence—Kenneth Mayer, M.D.

Tennessee

- Vanderbilt University, Nashville—Peter Wright, M.D.

Virginia

- University of Maryland, Fairfax—William Blattner, M.D.

Washington

- Fred Hutchinson Cancer Research Center and University of Washington, Seattle—Julie McElrath, M.D.

Washington, D.C.

- Johns Hopkins University Center for Immunization Research, Washington, D.C.—Donald Burke, M.D.

International

Africa

Botswana

- Botswana-Harvard Partnership for HIV Research and Education, Princess Marina Hospital, Gaborone—Myron Essex, D.V.M., Ph.D.

- Malawi College of Medicine, Blantyre—Taha E. Taha, M.D., Ph.D., and Richard Pendame, M.D.

South Africa

- South African Medical Research Council, Durban—Glenda Gray, M.D.

- Chris Hani Baragwanath Hospital, Soweto—Glenda Gray, M.D.

Asia

China

- Guangxi Health and Anti-Epidemic Center, Guangxi—Jie Chen, M.D.

India

- National AIDS Research Institute, Pune—Ramesh Paranjape, M.D.

Thailand

- Research Institute for Health Sciences, Chiang Mai—Thira Sirisanthana, M.D.

South America and the Caribbean

Brazil

- Hospital Escola Sao Francisco de Assis, Rio de Janeiro—Mauro Schechter, M.D., Ph.D.

- Centro de Referencia e Treinamento-DST/AIDS, Sao Paolo—Artur O. Kalichman, M.D., M.P.H.

Dominican Republic

- Centro Orientacion Integral/Instituto Dermatologica, Santo Domingo—Luis Moreno, M.D., and Claudio Volquez, M.D.

Haiti

- GHESKIO, Port-au-Prince—Jean William Pape, M.D.

Peru

- Associacion Civil Impacta Salud y Educacion, Lima—Jorge Sanchez, M.D., M.P.H.

Trinidad and Tobago

- Medical Research Foundation of Trinidad and Tobago, Port of Spain—Courtenay Bartholomew, M.D., FRCP

The **HPTN** domestic and international clinical sites and their principal investigators are as follows:

United States

Alabama

- University of Alabama at Birmingham—Sten Vermund, M.D., Ph.D.

California

- Los Angeles County Department of Health—Peter Kerndt, M.D., M.P.H.
- University of California at Los Angeles—Yvonne J. Bryson, M.D.
- University of California at San Francisco—Tsungai Chipato, MBChB

Maryland

- Johns Hopkins University, Baltimore—Robert C. Bollinger, M.D., M.P.H.
- Johns Hopkins University, Baltimore—David Celentano, Sc.D., M.P.H.
- Johns Hopkins University, Baltimore—Laura Guay, M.D.
- Johns Hopkins University, Baltimore—J. Brooks Jackson, M.D., M.B.A.
- Johns Hopkins University, Baltimore—Taha E. Taha, M.D., Ph.D.

Massachusetts

- Fenway Community Health, Boston—Kenneth H. Mayer, M.D.
- Harvard University School of Public Health, Boston—Wafaie Fawzi, M.D., Dr.P.H.

New York

- Columbia University Health Sciences, New York—Wafaa El-Sadr, M.D., M.P.H.

North Carolina

- University of North Carolina, Chapel Hill—Robert Ryder, M.D.

Pennsylvania

- University of Pennsylvania, Philadelphia—David Metzger, Ph.D.

Washington

- Harborview Medical Center, Seattle—Connie Celum, M.D., M.P.H.

International

Africa

Malawi

- Malawi College of Medicine, Blantyre—George Liomba, M.D.

South Africa

- South African Medical Research Council, Durban—Gita Ramjee, M.D.

Tanzania

- Muhimbili University, College of Health Sciences, Dar Es Salaam—Gernard Msamanga, M.D., D.Sc.

Uganda

- Makerere University School of Medicine, Kampala—Francis Mmiro, MBChB
- Makerere University School of Medicine, Kampala—Nelson Sewankambo, M.D.

Zambia

- Lusaka District Health Board and University Teaching Hospital, Lusaka—Moses Sinkala, M.D., and Chewe Lou, M.D., M.Sc.

Zimbabwe

- University of Zimbabwe, Harare—Tsungai Chipato, MBChB

Asia

China

- National Center for AIDS Prevention and Control, Beijing—Yiming Shao, M.D., Ph.D.

India

- IHI/YRG Care, Chennai—Suniti Solomon, M.D.
- National AIDS Research Institute, Pune—Sanjay M. Mehendale, M.D., MBBS, M.P.H.

Thailand

- Chiang Mai University, Chiang Mai—Chirasak Khamboonruang, M.D., Ph.D.

Europe

Russia

- St. Petersburg State University—Andrei Kozlov, Ph.D.

South America

Brazil

- Oswaldo Cruz Foundation, Rio de Janiero—Francisco Inacio Bastos, M.D.

Peru

- Universidad Peruana Cayetano Heredia, Lima—Jorge Sanchez, M.D., M.P.H.

Comprehensive International Program of Research on AIDS (CIPRA) Sites

CIPRA grants have been awarded to the following institutions and investigators.

Africa

Congo

- Congo National Laboratory of Public Health, Brazzaville—Blaise Bikandou, Ph.D.

South Africa

- University of Natal, Durban—Salim Karim Abdool, Ph.D.
- University of Witwatersrand, Johannesburg—James McIntyre, M.B.C.

Tanzania

- Kilimanjaro Christian Medical Centre, Moshi—John Shao, M.D., Ph.D.

Zimbabwe

- University of Zimbabwe, Harare—Lynn S. Zijenah, Ph.D., M.S.

Zambia

- Center for AIDS Research in Zambia, Lusaka—Isaac Zulu, M.D.
- Zambia Tropical Disease Research Centre, Ndola—Rosemary Musonda, Ph.D.

Asia

India

- Indian Council of Medical Research, New Dehli and Pune—Nirmal K. Ganguly, Ph.D.

Thailand

- Chiang Mai University, Chiang Mai—Thira Sirisanthana, M.D.

Vietnam

- Ho Chi Minh City AIDS Committee, Ho Chi Minh City—Le Troung Giang, M.D., Ph.D., M.P.H.

Cambodia

- Cambodian Health Committee, Phnom Penh—Sok Thim

Caribbean

Trinidad and Tobago

- Medical Research Foundation of Trinidad and Tobago, Port of Spain—Courtenay Bartholomew, M.D., FRCP

Dominican Republic

- Centro De Promocion Solidaridad Humano, Puerto Plata—Bayardo Gomez, M.D.

Europe

Russia

- Pavlov State Medical University, St. Petersburg—Edwin E. Zvartau, M.D., Ph.D.

North America

Mexico

- Mexico National Institute of Public Health, Cuernavaca—Jaime Sepulveda-Amor, Ph.D.

South America

Brazil

- Oswaldo Cruz Foundation, Rio de Janiero—Mariza G. Morgado, Ph.D.
- University of Caxias do Sul, Caxias do Sul—Ricardo D. De Souza, M.D., M.H.A.

Peru

- Asociacion Civil Impacta Salud y Educacion, Lima—Jorge L. Sanchez, M.D., M.P.H.

DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION

Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders, such as viruses, bacteria, and fungi, that may cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases, autoimmune disorders, primary immunodeficiencies, and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology and Transplantation (DAIT) *(www.niaid.nih.gov/dait)* promotes and supports a broad range of research that seeks to further our understanding of the immune mechanisms underlying immune-mediated diseases and to translate this basic knowledge to clinical applications that will benefit individuals affected by these diseases. The ultimate goal of DAIT's research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes of immune-mediated diseases and to apply this knowledge to the development of improved approaches to disease diagnosis, treatment, and prevention through demonstration and education research projects. DAIT evaluates the effectiveness of behavioral and educational interventions to promote health and prevent disease in defined populations.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further our understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

Scientific Areas of Focus

Asthma and Allergic Diseases

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. Studies to examine the causes,

pathogenesis, diagnosis, treatment, and prevention of allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment. In FY 2002, DAIT established the Inner City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children.

Autoimmune Diseases

DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease.

Basic and Clinical Immunology

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of the immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on a broad spectrum of diseases, including those that affect the intestines, joints, nervous system, and endocrine system. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune disease, and methods of immune intervention. In addition, support is provided for research on the causes and underlying immune mechanisms of various inherited immunodeficiency diseases, such as severe combined immunodeficiency disease.

Immune Tolerance

Immune tolerance is a high priority for NIAID, and as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN) in FY 1999. The ITN, cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, conducts clinical trials of promising tolerogenic approaches, carries out integrated studies of underlying mechanisms, and develops biomarkers and assays to measure the induction, maintenance, and loss of tolerance in humans. This international, multi-institutional research program is focused on four clinical areas: kidney transplantation, islet transplantation, autoimmune diseases, and asthma and allergic diseases.

Transplantation

The Division's basic research in transplantation immunology and genetics seeks to define the organization and effects of gene expression on immune function and to determine the manner in which the products of gene expression control the immune response to foreign

substances, such as transplanted organs and cells. In addition, DAIT supports individual research projects focused on the regulation of the immune response and program projects in transplantation immunology. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trials in Adult Kidney Transplantation and the Cooperative Clinical Trials in Pediatric Kidney Transplantation.

Primary Research Areas

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner City Asthma Consortium

Autoimmune Diseases

- Autoimmunity Centers of Excellence
- Autoimmune Diseases Prevention Centers
- Diabetes Centers of Excellence

Basic and Clinical Immunology

- Human Immunology Centers of Excellence
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Vaccine Immunology Basic Research Centers

Immune Tolerance

- Immune Tolerance Network
- Non-Human Primate Transplantation Tolerance Cooperative Study Group
- Innovative Grants in Immune Tolerance
- Innovative Research in Human Mucosal Immunity

Transplantation

- Cooperative Clinical Trials in Adult Kidney Transplantation
- Cooperative Clinical Trials in Pediatric Kidney Transplantation
- Immunopathogenesis of Chronic Graft Rejection

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports a wide variety of projects spanning the spectrum from basic biomedical research, such as studies of microbial physiology and antigenic structure, through applied research, including the development of diagnostic tests, experimental drugs, and vaccines, to conduct clinical trials to test the safety and efficacy of new disease prevention strategies. NIAID also funds projects to sequence the full genomes of a number of medically important microbes, which can be exploited in many ways, for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies on these pathogens extend basic insights to identify vaccine candidate antigens and drug targets and to examine mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include streptococci, pneumonia, nosocomial (hospital-acquired) infections, fungal infections, antibiotic resistance, bacterial sexually transmitted diseases (STDs), and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and reproduction of viruses; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic information is being used to combat important viral diseases such as influenza, herpes, congenital cytomegalovirus infection, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens and to the development of more effective drugs. In addition, studies of insect vectors are aimed at controlling the transmission of important pathogens such as malaria. Because parasitic and other tropical diseases are international health problems, the Division also supports clinical studies in regions where these infections are endemic through the Tropical Medicine Research Centers and International Collaboration in Infectious Disease Research programs.

An area of particular focus is emerging infectious diseases. The threat posed by disease-causing microbes may be expected to continue and even intensify in coming years. New infectious disease problems have continued to emerge recently, whether they are old diseases that have undergone dramatic increases, the new association of chronic diseases as sequelae of acute illnesses, opportunistic infections, viral infections most recently associated with cancers, or new diseases that are now impinging on the public consciousness. DMID, by supporting a broad spectrum of research in infectious diseases, has the capacity to focus the research agenda to understand the epidemiology, pathogenesis, and microbiology of emerging infections and infectious diseases and, ultimately, to develop mechanisms to control and prevent them. Examples include the emergence of new

infectious diseases, such as West Nile virus, hepatitis C, and *Helicobacter pylori*, and the re-emergence of old diseases, such as influenza and tuberculosis (TB).

Toward preventing disease, one of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents: bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

Internationally, DMID/NIAID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization (GAVI) and the Multilateral Initiative on Malaria (MIM). GAVI was established in 1999 as an alliance of global partners to replace the Children's Vaccine Initiative. The mission of GAVI is to save children's lives and protect people's health through the widespread use of safe vaccines.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for STDs and Lyme disease, and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies).

Scientific Areas of Focus

Emerging and Re-emerging Infectious Diseases

The threat posed by disease-causing microbes is expected to continue and even intensify in coming years. Infectious diseases have continued to emerge in recent years: diseases previously thought to be under control have undergone dramatic increases; new associations have been identified between chronic diseases and acute illness; opportunistic infections have arisen in immunosuppressed individuals; and previously unknown infections are now impinging on the public consciousness. Moreover, in the last year, we have witnessed the deliberate mailing of spores of anthrax bacterium, demonstrating our nation's vulnerability to agents of bioterrorism. In addition to anthrax, other potential agents of bioterrorism include smallpox virus, the bacteria that cause plague and tularemia, botulinum toxin, and filoviruses (for example, Ebola virus).

Factors that may explain the emergence of a new infectious agent include changes in the microbial agent, in the human population, in its behavior in the vector population, or in the ecologic relationships between these factors. Currently, recognized infections with potential for further emergence or re-emergence in more virulent forms, such as influenza, foodborne infections, hepatitis, and dengue, already cost the United States billions of dollars. DMID, by supporting a broad spectrum of basic, clinical, and epidemiologic research in infectious diseases, has the capacity to focus the research agenda to better understand the epidemiology, pathogenesis, and microbiology of emerging infectious diseases and ultimately to develop mechanisms of control and prevention.

NIAID's Network of Vaccine and Treatment Evaluation Units (VTEUs)

- Established in 1962
- >110 Phase 1, 2, 3 Clinical Trials since 1995
- Highlights
  - Childhood vaccines
  - Adult immunization
  - Combination vaccines
  - Novel delivery system
  - Vaccine safety
  - Challenge studies
  - Biodefense

Examples of DMID activities in this area include the research programs in hepatitis C virus, foodborne diseases, Lyme disease, arboviruses such as West Nile virus, and infectious agents most likely to be intentionally released as weapons of bioterrorism.

Vaccine Research and Development

One of the primary goals of the Division is to develop new and improved vaccines for preventing infectious diseases. Recombinant DNA technology, the production of monoclonal antibodies by hybridomas, nucleic acid sequencing, and peptide synthesis are providing researchers with new ways of producing more highly specific immunogenic antigens that can be incorporated into vaccines. These advances, coupled with the possibilities for manipulation of antibody and cellular immune responses, offer hope for preventing and ultimately eradicating many diseases that are not covered by current vaccines. These advances also enhance the possibility of improving the currently available vaccines.

Since 1981, DMID has supported a program for the accelerated development of new vaccines to take advantage of advances in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program has contributed to the development of new vaccines for *Haemophilus influenzae* type B, pneumococcal pneumonia, and pertussis (whooping cough). Among a longer list of research priorities for production of new and improved vaccines are those that protect against viral hepatitis, enteric pathogens (including rotaviruses and cholera), STDs, parasitic diseases, TB, and systemic fungal infections. The Division's *Jordan Report*, which provides an overview of the state of the science for vaccine research, can be viewed online at *www.niaid.nih.gov/dmid/vaccines/jordan20.*

DMID also supports research to develop novel vaccine delivery methods, such as transgenic plant vaccines (potatoes and tomatoes engineered to contain vaccine immunogens), transcutaneous skin patches, and nasal vaccines.

Clinical evaluation of vaccines is carried out through the DMID-supported Vaccine and Treatment Evaluation Units (VTEUs). This program is a national and international resource for evaluating promising new vaccine and treatment candidates in phase I, II, and III clinical trials. Studies conducted by VTEUs have led to the development of novel approaches in preventing and controlling a number of important pathogens, including influenza A and B viruses, parainfluenza viruses, rotaviruses, *H. influenzae* type B, hepatitis B viruses, cholera, and *Bordetella pertussis.*

Vaccine research and development are also important components of the Division's biodefense research agenda. The VTEUs have conducted several clinical trials to assess the feasibility of diluting the existing supply of smallpox vaccine while retaining vaccine efficacy. NIAID also supports research to develop and test future generations of smallpox and anthrax vaccines that may prove to be safer and more effective for use in the general public.

Antimicrobial Drug Resistance

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial compounds—are an increasingly important public health concern. TB, gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired (nosocomial) infections. Many physicians are concerned that several bacterial infections soon may be untreatable.

A key factor in the development of antimicrobial resistance is the ability of infectious organisms to adapt quickly to new environmental conditions. Microbes generally are unicellular creatures that, compared with multicellular organisms, have a small number of genes. Even a single random gene mutation can have a large impact on their disease-causing properties, and because most microbes replicate very rapidly, they can evolve rapidly. Thus, a mutation that helps a microbe survive in the presence of an antibiotic drug will quickly become predominant throughout the microbial population. Microbes also commonly acquire genes, including those encoding for resistance, by direct transfer from members of their own species or from unrelated microbes.

The innate adaptability of microbes is complemented by the widespread and sometimes inappropriate use of antimicrobials. Ideal conditions for the emergence of drug-resistant microbes result when drugs are prescribed for the common cold and other conditions for which they are not indicated or when individuals do not complete their prescribed treatment regimen. Hospitals also provide a fertile environment for drug-resistant pathogens. Close contact among sick patients and extensive use of antimicrobials force pathogens to develop resistance.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major healthcare-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the

molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. These efforts include epidemiologic research on major nosocomial pathogens such as *Staphylococcus aureus, Escherichia coli* species associated with urinary tract infections, and the *Enterococcus, Staphylococcus,* and *Streptococcus pyogenes*. These studies seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistance genes.

The Institute continues to participate in the ongoing interagency task force for the development of a public health action plan for antimicrobial resistance. Developed by an interagency task force cochaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the NIH, *A Public Health Action Plan to Combat Antimicrobial Resistance* states issues, goals, and action items in surveillance, prevention and control, research, and product development. Its goal is to ensure a comprehensive, coordinated response by Federal agencies and industry in addressing this critical health issue. The action plan is available online at *www.cdc.gov/drugresistance/actionplan/index.htm.*

Global Health

Key challenges facing global health efforts in the new millennium include the threat of emerging and re-emerging diseases (recent examples include West Nile virus in the United States, "mad cow" disease and new variant Creutzfeldt-Jakob disease in Europe, and the ever-present threat of pandemic influenza); the spread of drug resistance seen in all classes of microbial pathogens; the threat of bioterrorism; and the development of collaborative infrastructures and technologies to aid research and training at an international level.

To address these and other issues, NIAID has developed a comprehensive global health research plan. Many of these activities focus on vaccine development. Genomics, microbial physiology, epidemiology and natural history, and development of improved diagnostics and therapies also are important areas of emphasis. Diseases of international health importance also present additional scientific and logistical challenges, such as access to endemic sites and populations. The Institute supports field-based research through investigator-initiated grants, disease-specific initiatives, and special programs, such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

The Institute supports efforts to develop cost-effective, sensitive, and specific diagnostic tests; to develop new or improved chemotherapeutic approaches; to develop effective vaccines; and to control the transmission of disease by interfering with disease-bearing insect vectors. Investigations at the basic, clinical, and field levels are pursuing these efforts.

Tuberculosis

TB is a chronic infection of an estimated one-third of the world's population, including approximately 10 to 15 million persons in the United States. TB is the leading cause of death in the world due to a single infectious agent and will claim 30 million lives during the coming decade unless efforts to control its transmission are improved.[1] The link between HIV and TB is anticipated to be an increasingly important factor in the spread of TB. Current research is focused on the development of improved diagnostics, treatment, and vaccine strategies to control and prevent disease. The identification of factors associated with the transmission and

emergence of drug-resistant forms of TB is also a high-priority area. NIAID is actively engaged in advancing a national strategy for TB research and vaccine development through the *NIAID Global Health Research Plan on HIV/AIDS, Malaria, and Tuberculosis*. The Tuberculosis Research Unit (TBRU) supports an international, multidisciplinary team of collaborators to translate basic research findings into clinical studies.

Malaria

Malaria remains the most important of the tropical parasitic diseases in terms of annual mortality. Infection with these protozoan parasites, which are transmitted by mosquitoes, is a major public health problem in tropical and subtropical regions, where the disease exacts a heavy toll of illness and death. Although much effort has gone into controlling malaria in different parts of the world, initial successes have been reversed as a result of increased resistance of mosquitoes to standard insecticides, increased resistance of the malaria parasite to inexpensive and effective drugs, and changing epidemiologic and ecologic patterns resulting from economic development within malarious areas. The magnitude of the problem and existing barriers to control efforts require new approaches, including the use of vaccines, for prevention and treatment of malaria. Malaria is a high-priority research area for the Division, as is demonstrated by the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. Current research activities sponsored by NIAID include drug development, pathogenesis research, vaccine development, and epidemiology and vector control. NIAID's *Research Plan for Malaria Vaccine Development*, which describes the Institute's goals and plans for developing a malaria vaccine, can be viewed online at *www.niaid.nih.gov/dmid/malaria/malvacdv/toc.htm.*

Influenza

Each year, 10 to 20 percent of Americans get sick with the flu (influenza). For most individuals, fever, exhaustion, and aches and pains of the flu can be debilitating for 1 or 2 weeks, but for older persons and those with compromised immune systems, the flu can be much more serious. An estimated 100,000 hospitalizations and about 20,000 deaths occur each year from the flu or its complications *(www.niaid.nih.gov/newsroom/focuson/flu.htm)*.

The influenza virus, which causes the flu, keeps coming back each year because it continually changes; subtle genetic mutations allow new strains of the virus to infect people who would otherwise be immune because of prior infection or vaccination. Occasionally, the influenza virus undergoes a more dramatic genetic change that causes it to become even more infectious, triggering a global pandemic.

The major goal of DMID's influenza program is to stimulate research that may lead to more effective vaccines and treatments that will better control future influenza virus infections and reduce the risk of another major influenza pandemic.

Sexually Transmitted Diseases

STDs are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. Scientists now believe that people who have STDs are at an increased risk of

[1] NIAID/NIH Workshop Report. *Blueprint for tuberculosis vaccine development*. B. Bloom, ed. March 5-6, 1998; World Health Organization (WHO). *Global tuberculosis control*. WHO Report 2001. Geneva, Switzerland.

contracting HIV/AIDS. DMID's STD research emphasis is on vaccine development and on clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STDs and conditions associated with having STDs, for example, pelvic inflammatory disease (PID), infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and the spread of HIV. NIAID also supports a topical microbicide research effort to prevent STDs; this effort encompasses basic, product development, and clinical research.

Pathogen Genomics

In 1995, the first microbe sequencing project, *H. influenzae* (a bacterium causing upper respiratory infection) was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and includes projects to sequence the full genomes of many pathogens, including the bacteria that cause TB, gonorrhea, chlamydia, and cholera. In addition, NIAID collaborates with other funding agencies to sequence larger genomes of protozoan pathogens, such as the organism causing malaria.

The availability of microbial and human DNA sequencing will open up new opportunities and allow scientists to examine functional analysis of genes and proteins in whole genomes and cells, as well as the host immune response and an individuals' genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins, or to use those proteins as candidates for vaccine testing. Genetic variations can also be used to study the spread of a virulent or drug-resistant form of a pathogen.

As a consequence of the Institute's increasing commitment to genomics activities, NIAID's Blue Ribbon Panel on Genomics has established a policy for support of large-scale genome sequencing projects and includes priority organisms for large-scale sequencing projects. The ultimate goal is to foster the burgeoning field of pathogen genomics, which, supported by the development of various new technologies, continues to uncover clues to microbial functioning that hold promise for the prediction of disease progression and for patient care and treatment, translating genomic information into clinical applications.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate sequence and functional data.

In summary, DMID supports a breadth of research activities on a variety of pathogens of importance in basic microbiology and infectious diseases.

DIVISION OF INTRAMURAL RESEARCH

Mission

Scientists in NIAID's Division of Intramural Research (DIR) *(www.niaid.nih.gov/dir)* conduct laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. For example, DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, parasites, and fungi that cause infectious diseases. They also study the ticks, mosquitoes, fleas, and flies that transmit diseases such as West Nile fever, plague, and malaria. In addition, DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

Much of the research in DIR involves investigation of the multitude of interacting cells, antibodies, receptors, proteins, and chemicals that compose the immune system. A fundamental understanding of this intricate system is key to the development of therapies and vaccines for infectious diseases, and critical to deciphering and treating immune system disorders—from mild allergies to life-threatening immune deficiencies. The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that will improve health, save lives, and enhance the quality of life in the United States and worldwide. This contribution may take the form of delineating a cell signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency.

Translating laboratory research findings to the clinical arena is accomplished through the facilities of the Warren Grant Magnuson Clinical Center on the NIH campus. There, physician-scientists treat patients with a variety of diseases, including AIDS, vasculitis, immunodeficiencies, host defense defects, unusual fungal infections, asthma, allergies, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 15 DIR laboratories *(www.niaid.nih.gov/dir/labs.htm)* has project-specific resources that are augmented by the

expertise and services provided to all DIR labs by five supporting branches. For example, the branches ensure that DIR investigators have access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, and DNA microarray. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive in-house animal breeding and holding facilities (including nonhuman primate), oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities, including biosafety-level-three facilities, are maintained in Bethesda, Maryland, and at DIR laboratories in Hamilton, Montana. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility. Investigators wishing to interact directly with other scientists in a very focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of the NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine, and links DIR researchers in the Maryland locations of Bethesda, Rockville, and the Frederick Cancer Research and Development Center, and in the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff members and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are much faster and more dependable than the local Internet service provider connections.

Scientific Areas of Focus

Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Much of the research focuses on the B and T lymphocytes, which react to foreign organisms that have entered the body. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the lymphocytes are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Recent studies include the following:

- Role of adenosine in inflammation control,
- Structural analysis of T-cell and NK-cell receptors,
- Discovery of cellular receptors associated with lower risk of kidney transplant rejection, and
- Gene therapy for immunodeficiencies.

Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. DIR studies include the following:

- Cytokine profiles of allergic diseases,
- Tolerance studies for asthma,
- Mouse models of allergic diseases, and
- Efficacy of a soluble interleukin-4 receptor in treating asthma.

Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, the host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies may reveal new targets for public health interventions. DIR investigators also are studying potential infectious etiologies of chronic diseases. Several infectious agents, such as hepatitis C virus, human papillomavirus, and *Chlamydia pneumoniae*, have been associated recently with chronic illnesses. Examples of ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy,
- Development of more effective drugs for tuberculosis,
- Pathogenesis and cross-species transmissibility of prion diseases or transmissible spongiform encephalopathies, and
- Genetics of drug resistance, antigenic variation, and disease severity in malaria.

Vaccine Research

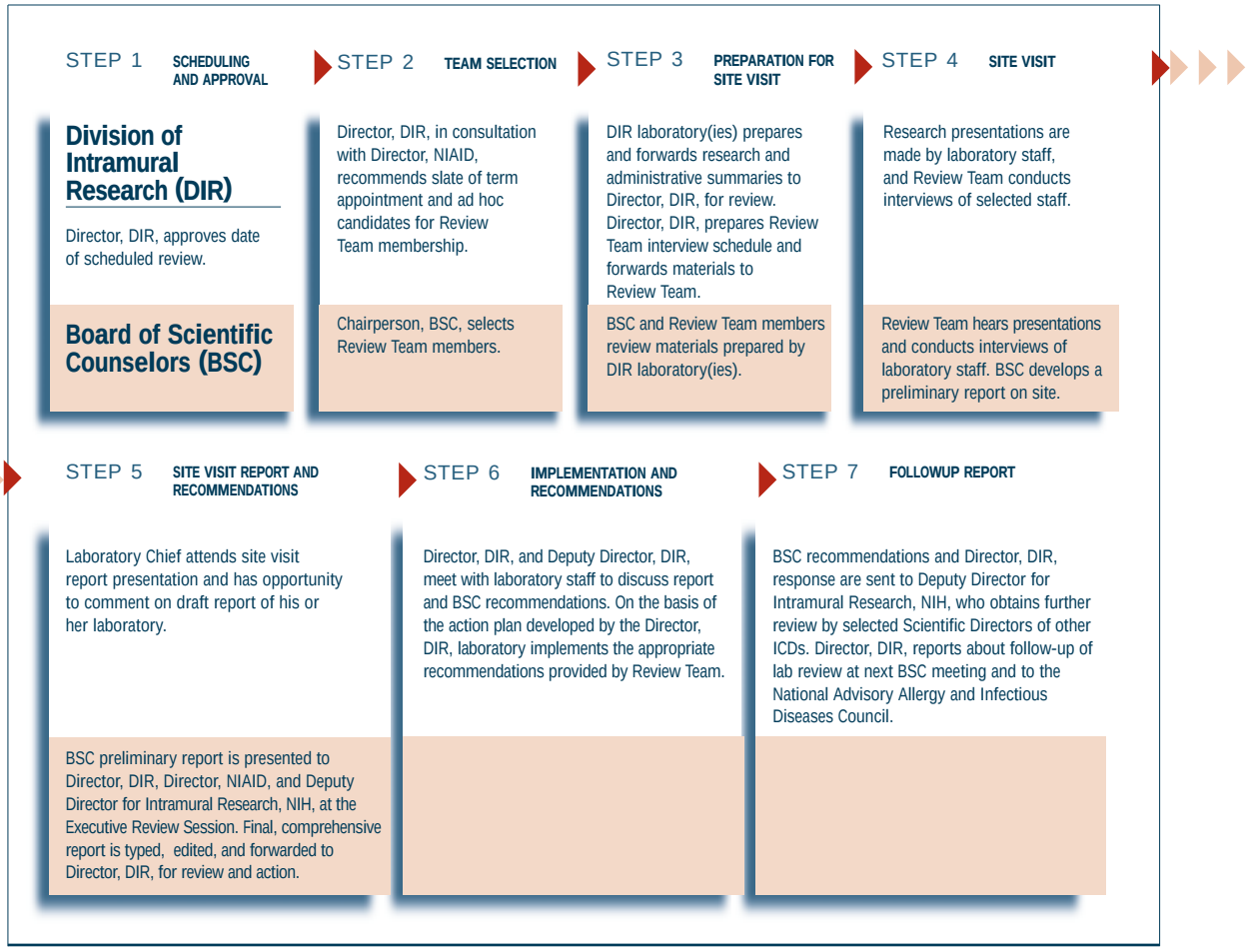
DIR researchers are developing several new and novel vaccines, such as those that might be able to immunize people against more than one disease at the same time. Another example of a novel vaccine is the transmission-blocking vaccine for malaria, which would prevent a mosquito that had just bitten a malaria-infected person from transmitting the malaria parasite to other individuals. Studies are under way to develop vaccines against pathogenic flaviviruses, such as the West Nile virus, dengue, and tick-borne encephalitis virus. Investigations continue toward the development of a vaccine against the respiratory syncytial

virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR.

Laboratory Review Process

The following chart provides information on DIR's laboratory review process:

DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) *(www.vrc.nih.gov)* is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of the VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated five million new HIV infections each year, and in 2001, HIV/AIDS was the fourth overall leading cause of mortality worldwide, resulting in an estimated three million deaths.[1] Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Therefore, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that may lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, the VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that may limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

While development of an effective vaccine against HIV remains the primary mission of the

[1] UNAIDS and World Health Organization. *AIDS epidemic update*, December 2001. *www.unaids.org/epidemic_update/report_dec01/index.html#full.*

VRC, ongoing VRC research programs in biodefense have been expanded, intensified, and accelerated. For example, the VRC is positioned to make substantive contributions in the development of vaccines for smallpox and viral hemorrhagic fevers. The VRC is working closely with the NIAID Division of Microbiology and Infectious Diseases to help develop a safer smallpox vaccine. Viral hemorrhagic fevers, such as Ebola, Marburg, and Lassa, also may present a potential bioterrorist threat. To meet this threat, the VRC is developing candidate vaccines for preclinical and clinical testing.

Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this process has been successful for numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology is now emerging that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance. By having diverse components of vaccine research, development, production, and evaluation readily accessible at one site, along with a group of committed investigators with diverse skills but a common goal, the VRC has embarked on a comprehensive and systematic approach to vaccine development.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, will be established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, the VRC hopes to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine and for an effective Ebola vaccine.

Research Goals and Objectives

The VRC has four broadly encompassing research goals, each of which has multiple subparts. The goals are as follows:

- Goal 1: Scientifically design and develop effective vaccine candidates
  - Use knowledge of the HIV envelope structure to design immunogens that elicit potent virus-neutralizing antibodies through a program of rational structure-based design and screening of immunogens
  - Develop and optimize gene-based vaccine platforms that elicit broad and potent cell-mediated and humoral immunity

- Use state-of-the-art methods in genomics and bioinformatics to advance vaccine development

- Goal 2: Evaluate and optimize the immune response generated by candidate vaccines
  - Identify and develop validated, reproducible methods to quantitate vaccine-induced immune responses in humans and primates
  - Identify vaccine candidates and immunization strategies that enhance potency, antigen presentation, and immunogenicity
  - Develop rational use of the primate model to assess vaccine strategies and define immune correlates
- Goal 3: Advance the most promising vaccine candidates into human clinical trials
  - Develop the infrastructure to produce and test vaccine products
  - Conduct clinical evaluation of candidate vaccines
  - Evaluate preventive vaccine candidates in clinical protocols of therapeutic immunization
- Goal 4: Create the necessary infrastructure for translating basic research to the clinic

  Establishment of a Vaccine Pilot Plant (VPP) is a high priority for the VRC. The VPP will manage production of multiple vaccine candidates originating from the VRC. To achieve this objective, the VPP will function in concert with the Vaccine Production Laboratory located on the Bethesda campus in transferring new vaccine technology for pilot-scale production of clinical trial material. The VPP will be designed as a leased pilot plant in Frederick, Maryland, with an anticipated completion date of late 2004. Vaccines produced at the VPP will support phase I and II clinical trials. In addition, the facility will incorporate design features that will allow conversion to larger scale operations capable of supporting phase III trials, if necessary.

Basic Research

Acquired Immunodeficiency Syndrome

The VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Recent data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program will explore basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at the VRC will apply this knowledge toward the design of vaccines. A program in virus structural biology will explore the rational design of vaccines that can induce potent virus-neutralizing antibodies. Development of candidate vaccines will focus on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered using immunization with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral

vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines. Such preclinical animal testing is closely integrated with the VRC's basic science programs to provide information for iterative improvements in the development of new candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV will be guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. Reproducible, validated assays to measure T-cell function and virus particle reduction will be developed and applied to animal studies and human clinical trials. In this way, scientists can determine how effectively the candidate vaccine protects against infection or disease. Preclinical studies in small animals and primates will evaluate vaccine dose, formulation, and delivery route and will address the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be integrated closely with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

Ebola and Other Viral Hemorrhagic Fevers

The Ebola virus is associated with an aggressive course of infection, hemorrhagic fever, and a high mortality rate, particularly for the Ebola Zaire subtype. Because the natural reservoir for Ebola virus is unknown, traditional public health measures to prevent future outbreaks are limited, thus increasing the urgency for development of an effective vaccine. Previously, it had been shown that immunization with DNA-encoding Zaire-subtype glycoprotein (GP[Z]) yielded a significant humoral protective response in guinea pigs. The VRC carried out additional studies and determined that a prime-boost strategy, with naked DNA as prime (initiation of an immune response) and recombinant adenoviral vector as boost (enhancement of the initial immune response) substantially enhanced the immune response.

The VRC will continue to develop and test multivalent vaccines to evaluate their protection against multiple hemorrhagic fever pathogens of natural or deliberate infections.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, the VRC will combine traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach will

promote an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, the VRC will study the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T-cell memory that play a role in protection against HIV. Such data can then be applied to the development of therapeutic and preventive vaccines.

The VRC will actively collaborate with intramural and extramural scientists and facilitate the movement of ideas from the broader community into clinical trials. The VRC will maintain close ties with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials is already established. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, the VRC also will interact with the pharmaceutical industry, in which there is a large capacity for, and experience in, product development and distribution. Therefore, the VRC will fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

The VRC expects to conduct three to six phase I trials per year. Currently, one HIV vaccine clinical trial is under way, with an additional trial scheduled for fall 2002. In addition, plans call for a modified vaccinia virus Ankara (MVA) phase I clinical trial to open in the fall, with another MVA trial opening in the spring. It is hoped that MVA will serve as a component of a safer smallpox vaccine.

Human Clinical Trials and Licensure of an AIDS Vaccine

The VRC will work closely with its scientific collaborators and with the Food and Drug Administration to discuss the potential for expedited approval of AIDS vaccines. The carefully considered use of surrogate end points (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate end points can accrue from well-designed trials, and this information can be applied to the design of future trials.

DIVISION OF EXTRAMURAL ACTIVITIES

Mission

The Division of Extramural Activities (DEA) *(www.niaid.nih.gov/ncn)* serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training program, and conducting initial peer review for funding mechanisms with Institute-specific needs. DEA also provides broad policy guidance to Institute management and oversight of all of NIAID's chartered committees. The Office of the Director, DEA, is a long-time leader of NIH reinvention experiments, including the creation of innovative electronic systems that have changed NIAID and NIH operations.

DEA staff members in every part of the organization interact intensively with grantees, contractors, reviewers, members of the National Advisory Allergy and Infectious Diseases Council (NAAIDC), and applicants, as well as with the staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome, the Division of Allergy, Immunology and Transplantation, and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch issues all NIAID grant awards after negotiating the terms of the grant award with the applicant. Specialists in the Branch determine the amount of the award, develop the administrative terms and conditions, and release the official award document. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowable and how to formulate a budget for a grant application. Grant specialists supervise the day-to-day administration and financial management of Institute grants and cooperative agreements, while ensuring that NIAID's grants are in compliance with existing policies. They are sources of valuable information on existing and new policies that may alter a grantee's requirements and privileges and that can inform grantees about which actions need approval and from whom.

Contract specialists manage the administrative aspects of NIAID's research and development contract portfolio. Toward those ends, they help develop requests for proposals, negotiate the technical and business aspects of proposals, and select the proposals. Working in DEA's Contract Management Branch (CMB), contract specialists are well versed in a full range of legal, technical, business, and cost-related topics, including Federal Acquisition Regulations and other policies and procedures. They provide investigators with guidance on changes in the scope of the research, the allowability of costs, and other administrative issues, including the use of contract funds, the technical or administrative performance of a contract, current or anticipated initiatives, and changes to a contract. More information about contracts is available at *www.niaid.nih.gov/contract.*

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications and requests for proposals. Working in DEA's SRP, Institute review staff members assist investigators and NIAID staff members with issues related to grant and proposal preparation, including application

format and documentation requirements. They also can provide insights into the peer review process and plans for specific review meetings; give advice on applying for a grant, including special review criteria and other requirements of NIAID program announcements, requests for applications, and requests for proposals; answer questions about the assignment or scheduling of applications or proposals for review; and advise applicants on NIH policy requirements. SRP manages NIAID's three chartered review committees and convenes special emphasis panels as needed.

DEA's Referral and Program Analysis Branch (RPAB) is the Institute's referral point for grant applications. RPAB also performs scientific classification and data analysis of all funded grants, contracts, and intramural research projects, including the categorization and analysis needed to generate official NIAID science-information reports.

Several offices and staff members in DEA's Office of the Director play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including small business programs (Small Business Innovation Research [SBIR] and Small Business Technology Transfer [STTR]), Academic Research Enhancement Award (AREA) grants, Council activities, and extramural communications. They develop policies and processes for NIAID's extramural research programs, including innovative electronic systems, and provide guidance on grant requirements and procedures to investigators.

The Office of Special Populations and Research Training (OSPRT) oversees NIAID's portfolio of training grants, fellowships, and career development awards. Staff members in this Office answer questions that applicants have about training-type support awards supported by NIAID. In addition, OSPRT administers the Research Supplements for the Underrepresented Minorities Program, which supports young minority scientists on NIAID-funded research grants.

The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, special emphasis panels, and three review committees.

To keep the Institute's extramural research community informed and to provide advice on many research and policy topics, DEA produces the NIAID *Council News* newsletter and sponsors the *Council News* Extramural Information Center on the World Wide Web *(www.niaid.nih.gov/ncn)*. These outreach resources keep grantees, applicants, and staff members up to date on Institute funding opportunities, policy changes, and other news. They also educate our extramural constituency by providing budget and payline information, a glossary of NIH terms and acronyms, articles on complex subjects such as percentiling, and advice on writing a grant application.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Significant progress has been made in HIV/AIDS research since 1981 when AIDS first emerged as a global infectious disease. Research has led to a better understanding of the structure of HIV, how HIV attacks the immune system, the role of the immune system in controlling HIV infection, and how to intervene therapeutically. Potent therapeutic regimens, commonly referred to as highly active antiretroviral therapy, or HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and in decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected people in the United States and has led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the HIV/AIDS pandemic continues to rage around the world, with more than 40 million people (37.1 million adults and 3 million children) living with the disease. In 2001, 3 million people died from AIDS, and 5 million people were newly infected with HIV. Of the 5 million new infections, 800,000 were in children. More than 95 percent of new HIV infections occur in the developing world, with 70 percent occurring in sub-Saharan Africa and 20 percent in Asia and the Pacific. Most of these new infections are in young adults, with an increasing number among women.[1] In the United States, close to 950,000 people are living with HIV/AIDS, and each year 40,000 new infections occur, of which more than one-half are in individuals younger than 25 years of age.[2]

Since the beginning of the epidemic, NIAID's comprehensive research program has been at the forefront in the fight against AIDS. NIAID supports a broad array of domestic and international HIV/AIDS research programs and collaborates with more than 40 countries through investigator-initiated research grants and multicenter prevention, vaccine, and therapeutic research networks.

With a growing number of research programs and initiatives, NIAID is poised to tackle new research challenges and the changing demographics of the HIV/AIDS epidemic. To address HIV/AIDS research needs in developing countries, NIAID initiated the Comprehensive International Program for Research on AIDS (CIPRA) *(www.niaid.nih.gov/daids/cipra)*. In the past year, 11 additional R03 awards were made (Brazil, Cambodia, Congo, the Dominican Republic, India, Mexico, Tanzania, Thailand, Vietnam, Zambia, and Zimbabwe) as well as 3 large multiproject awards to institutions in Beijing, China; Johannesburg, South Africa; and Durban, South Africa. These grants will provide support to developing countries to plan and implement comprehensive HIV/AIDS prevention and treatment research agendas relevant to their populations, to enhance the infrastructure necessary to conduct such research, and to participate in collaborative, multicenter clinical trials.

Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV subtypes is the ideal prevention strategy and one of NIAID's highest priorities. To accelerate vaccine development worldwide, NIAID established the HIV Vaccine Trials Network (HVTN). The HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate HIV vaccines. The HVTN has

expanded this past year, adding sites in Malawi and Brazil. Plans are also under way to add sites in Jamaica and Honduras as well as in the United States. Currently, there are 18 U.S. sites and 13 international sites. (For a listing of the HVTN locations, see page 17.) In addition, NIAID will be working much more closely with the Department of Defense HIV Research and Development Program of the United States Army Medical Research and Materiel Command (USAMRMC). NIAID's HIV vaccine efforts are described in more detail in the Vaccine Research and Development material beginning on page 127.

Nonvaccine Prevention Research

To control the HIV epidemic, new and more effective methods and strategies are needed for preventing HIV infection. Until a highly efficacious vaccine, or even a partially protective vaccine, is developed that can be widely distributed and used, control of the epidemic will require a combination of prevention approaches. NIAID established the HIV Prevention Trials Network (HPTN) to develop and test promising nonvaccine strategies to prevent the spread of HIV/AIDS. The HPTN includes 15 domestic sites and 14 international research sites. (See the map on page 15.) The HPTN evaluates the efficacy of promising biomedical and behavioral interventions for the prevention of HIV, including the following:

- Drugs or vaccines that are practical and easy to use to prevent mother-to-child transmission (MTCT) of HIV, including prevention during breastfeeding;
- Microbicides to prevent sexual transmission of HIV (see Topical Microbicides in the Sexually Transmitted Diseases material on page 117);
- Antiretroviral therapy (ART) that may reduce the spread of HIV from infected persons to their sexual partners;
- Measures to control other sexually transmitted diseases and thereby decrease the risk of co-infection with HIV;
- Interventions to reduce behavior that exposes people to HIV; and
- Programs to curb the spread of HIV by reducing intravenous drug abuse.

NIAID-funded research through the HPTN and other sources of support has led to important scientific advances that increase our understanding about the transmission of HIV. These findings provide a foundation for developing and testing innovative prevention strategies. Recent findings include the following:

- Data establish the continued benefit and safety of giving nevirapine to mothers and their newborn infants to reduce perinatal HIV transmission through 18 months, even in a breastfeeding population.
- Additional data indicate that nevirapine resistance fades from detection in both women and infants over time.
- Stronger evidence exists that early circumcision may reduce men's risk of HIV acquisition during unprotected sexual contact later in life.
- Preliminary data from a phase II study of Carraguard™, a novel vaginal microbicide, reveal that it is safe and well tolerated in sexually active, uninfected women.

- Phase II studies show that two microbicides, BufferGel® and PRO 2000/5 Gel, are relatively safe and acceptable for use in HIV-infected men. A phase III efficacy and effectiveness trial in women is planned for FY 2003.

Therapeutics

The increased life expectancy of HIV-infected individuals as a result of HAART has resulted in more individuals living with the disease, as well as a host of complications resulting from the therapeutic regimen. These complications include the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by HAART. Thus, there continues to be an urgent need for new therapeutic entities and approaches to expand the number and clinical benefit of currently approved therapies. NIAID's therapeutics research programs and networks are focusing on these issues.

NIAID is currently conducting a long-term study to address important questions about the most appropriate use of currently available antiviral drugs for the treatment of HIV/AIDS. This study, Strategies for Management of Anti-Retroviral Therapies, or SMART, will determine which of two common HIV treatment strategies result in a better outcome over time. The SMART study is among the first long-term studies of its kind and is being conducted through the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). This study will be conducted over a 9-year period and will eventually involve 6,000 patients. More than 600 HIV-infected people have already been enrolled in the study. The SMART study is designed to ultimately provide information that will help physicians and their patients make informed treatment decisions. For more information about the SMART study, please visit *www.smart-trial.org*.

NIAID researchers have found a beneficial effect in the immune response when antiretroviral therapy was interrupted repeatedly. This approach has important implications for the long-term use of antiretrovirals and could decrease both the cost and side effects of treatment.

A major goal of NIAID intramural researchers and their collaborators is to discover new therapies for AIDS that are less expensive or less toxic than current therapies and, therefore, have the potential for more widespread use. Several new approaches are under study in NIAID's Division of Intramural Research (DIR). For some HIV-infected patients whose plasma levels of virus have fallen to undetectable levels while on HAART, it may prove feasible to move from a continuous HAART regimen to intermittent therapy in which an individual discontinues then resumes HAART in a preplanned cyclic fashion. This cyclic approach to treatment, known as structured intermittent therapy, might enable an HIV-infected person to have regular HAART-free periods while maintaining a minimal viral load and adequate levels of CD4+ T cells.

To test this concept, DIR researchers conducted a 68-week pilot study in which the regimen of structured intermittent therapy maintained suppression of both viral particles in the blood and HIV replication in reservoir sites while preserving CD4+ T-cell counts.[3] In addition, study volunteers experienced a decrease in important toxicity parameters and significantly lower cholesterol and triglyceride levels, which are often abnormally elevated in patients on

HAART. Larger clinical trials are under way to address the efficacy and impact of this short-cycle intermittent therapy.

Although HAART has dramatically improved the clinical outcome for many HIV-infected patients, the associated cost, toxicity, and development of drug resistance underscore the need for additional therapeutic strategies. Strategies aimed at enhancing the ability of the immune system to fight HIV infection are under investigation by NIAID intramural scientists and others as potential supplements to antiretroviral therapy. These immune-based strategies include treatments that stimulate or suppress a particular part of the immune system, infusion of additional immune system cells, and therapeutic immunizations. NIAID's long-term basic research into the function of interleukin-2 (IL-2) in the immune system and clinical studies of its safety and efficacy for HIV therapy have led to promising results. Randomized phase III clinical studies by NIAID intramural investigators, as well as two large international studies, are ongoing to clarify the effect of IL-2 on viral load and CD4+ counts and to assess long-term clinical outcomes.[4]

The next generation of antiviral therapeutics may include entry inhibitors that prevent HIV from attaching to CD4+ T cells. Infection of these cells by HIV is a complex process that starts with attachment of the virus to a CD4 molecule on the outside surface of the cell. However, past attempts to develop inhibitors of viral entry failed, in part because they were unable to efficiently prevent HIV from attaching to the CD4+ T cells. Moreover, at low levels these inhibitors actually enhanced the ability of HIV to infect CD4+ T cells.

NIAID researchers have constructed a compound that inhibits entry of HIV into CD4+ T cells and does not enhance HIV entry under any conditions. This compound is a large protein that binds specifically to the part of HIV that attaches to the CD4+ T cells. The protein exhibited extraordinarily strong binding to HIV, and relatively small amounts were able to neutralize HIV samples from a broad range of infected patients.[5] This finding is an important step toward development of drugs targeting viral entry, a mode of action not represented in the current antiretroviral arsenal.

ANTIMICROBIAL RESISTANCE

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial compounds—are an increasingly important public health concern. Antimicrobial resistance has become a significant public health problem because of overuse of antimicrobial drugs and failure to ensure proper diagnosis, drug use, and adherence to treatment. The most serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and urinary tract infections. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the need to use more and broader spectrum drugs to clear resistant infections, untreatable infections leading to increased morbidity and mortality, and an increase in selective pressure leading to the spread of resistant organisms.

This phenomenon is prevalent in developed countries and also is a challenge for developing areas of the world. Factors in the emergence of resistant malaria parasites, diarrheal pathogens, and sexually transmitted bacteria include incomplete or inadequate antimicrobial therapy, ineffective counterfeit drugs, and lack of access to health care. New prevention and treatment strategies are needed, as well as making effective use of the tools currently available for fighting resistant infectious diseases.

Hospitals are a critical component of the antimicrobial resistance problem. Many factors are believed to contribute to the emergence of drug resistance among nosocomial pathogens, including overuse of broad spectrum agents, increasing numbers of susceptible and immunocompromised patients, use of invasive procedures and devices, and the breakdown of infection- and disease-control practices. As a result, methicillin-resistant *Staphylococcus aureus* (MRSA) has increased to 53.5 percent and methicillin-resistant coagulase-negative staphylococci to 88.2 percent. Increasing reliance on vancomycin has led to the emergence of vancomycin-resistant enterococci (VRE), bacteria that infect wounds, the urinary tract, and other sites. VRE has increased to 24.7 percent in intensive care units (ICUs) in the United States.[6]

One of the most disturbing trends is the movement of multi-drug-resistant pathogens out of the hospital setting into the community. MRSA, long a problem in ICUs and nursing homes, is an emerging community-acquired pathogen among patients without histories of hospital stays or previous infections. Four recently reported cases of MRSA in children were community acquired, resulted in death, and show the potential severity of this phenomenon.[7]

Streptococcus pneumoniae (pneumococci) causes thousands of cases of meningitis and pneumonia and 7 million cases of ear infection in the United States each year, and multi-drug-resistant pneumococci are common and increasing. Overall, 24 percent of isolates causing invasive disease are resistant to penicillin, with averages as high as 35 percent in some States. Penicillin-resistant isolates also show resistance to other antimicrobial agents.[8]

An estimated 300 to 500 million people worldwide are newly infected with the parasites that cause malaria, and an estimated 1 million people die every year from this infection. Resistance to chloroquine, once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.[9]

The incidence of multi-drug-resistant tuberculosis (MDR-TB) has increased dramatically in the past decade and is currently present on five continents. Infection with TB in people also infected with HIV is occurring in several regions, in particular Africa and Asia, with negative impact on clinical outcome. Drug-resistant strains are as contagious as those that are susceptible to drugs and often reflect mismanagement of therapy. MDR-TB is more difficult and vastly more expensive to treat, and patients may remain infectious longer because of inadequate treatment.[10]

Diarrheal diseases cause almost 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae*, *Salmonella typhimurium*, and *Vibrio cholerae*, are emerging. Worldwide, shigella has become progressively resistant to most of the widely used inexpensive antibiotics. Multiple-resistant strains have occurred in Latin America, Central Africa, and Southeast Asia. *S. dysenteriae* type 1 is now uniformly resistant to almost all first-line agents.[11]

There is increasing evidence that the use of antimicrobials in food animals is associated with the emergence of resistance among *Salmonella* and *Campylobacte*r isolated from the meat of animals.[12] In response to this threat, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance, as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports a number of clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these networks are the AIDS Clinical Trials Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Unit, and the recently established Bacteriology and Mycology Study Group, with one unit directed toward serious resistant bacterial infections.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. In fiscal year 2002, NIAID announced an initiative called Partnerships for Novel Therapeutics and Vector-Control Strategies in Infectious Diseases, with the goal of supporting partnerships to develop new drugs and diagnostics in areas that are not currently a high priority for industry but are likely to have a high impact on public health. In addition, NIAID released a new initiative designed to encourage the development of innovative approaches to combating antimicrobial resistance.

NIAID cochairs an Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration; several other Government agencies also are represented on this task force. In June 2002, a public meeting was held to provide a first-year summary of accomplishments associated with *A Public*

Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues. First published in January 2001, the action plan reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, which is based on input from constituents and stakeholders and serves as a blueprint for specific coordinated Federal actions. The action plan is available online at CDC's antimicrobial resistance Web site: *www.cdc.gov/drugresistance*. A companion piece on international issues is being developed by this interagency group in collaboration with the World Health Organization and other partners.

NIAID also investigates antimicrobial resistance in its Division of Intramural Research (DIR). In laboratory and clinical studies, DIR scientists study the organism and the host to elucidate the factors contributing to resistance to a variety of antimicrobial drugs. Intramural scientists and their collaborators deciphered the evolution of drug resistance to a class of compounds used clinically in the developing world to treat TB. DIR scientists are now examining the relapse of patients who fail conventional TB chemotherapy to develop an understanding of why they fail chemotherapy and to define the factors involved in the development of multiple drug resistance in tuberculosis. In addition, DIR investigators and their collaborators discovered the gene responsible for chloroquine resistance and have recently furthered this discovery by mapping the specific mutations underlying resistance to position 76 of the vacuolar transmembrane protein PfCRT.[13]

DIR scientists also are studying the contribution of biofilms—communities of microorganisms embedded in a mucoidal (slime) matrix—to drug resistance. A bacterium often associated with biofilms, *Staphylococcus epidermidis*, is the most common pathogen in hospital-acquired infections and is responsible for health care costs of more than 1 billion dollars per year. Although usually a harmless bacterium of human skin, *S. epidermidis* may cause septicemia or endocarditis in patients undergoing immunosuppressive therapy, premature newborns, or injection drug users. However, most infections occur after the insertion of indwelling devices such as catheters or prosthetic heart valves. In these cases, the ability of *S. epidermidis* to form biofilms represents the most important virulence determinant. In a biofilm, the bacteria are dramatically less susceptible to antibiotic treatment and to attacks by human immune defenses. For these reasons, *S. epidermidis* infections are very difficult to eradicate. DIR scientists propose that drugs preventing and/or targeting biofilm formation will be of extraordinary use in antistaphylococcal therapy because they will enable the immune system to cope with an infection and increase the efficiency of common antibiotics. To provide the scientific basis for the development of drugs interfering with biofilm formation, DIR scientists are investigating the molecular biology, biochemistry, and epidemiology of biofilm formation. This investigation includes studying specific factors contributing to biofilm formation, their regulation, and the interaction of biofilm-forming *S. epidermidis* strains with the host.

ASTHMA AND ALLERGIC DISEASES

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Chronic allergic conditions can significantly decrease quality of life, patient well-being, employee productivity, and school performance and attendance. Estimated annual health care costs are more than $14 billion. NIAID's goal in asthma and allergic diseases research is the development of more effective treatments, prevention strategies, and behavioral interventions.

Approximately 50 percent of Americans have positive skin tests to at least 1 of 10 allergens known to contribute to allergic illness.[14] These allergens include ragweed, Bermuda grass, rye grass, white oak, Russian thistle, Alternaria, cat, house dust mite, German cockroach, and peanut. The prevalence of allergic rhinitis (hay fever) varies widely among different countries, from 2 to 40 percent.[15] The prevalence of allergic rhinitis has increased substantially over the past 15 years[16] and is estimated to be 9.9 to 16 percent in the United States.[17-18]

Atopic dermatitis is one of the most common skin diseases worldwide, particularly in infants and children. The prevalence of atopic dermatitis varies widely in different countries, from 1 to 15 percent. The estimated prevalence of atopic dermatitis in the United States is 9 percent[19] and appears to be increasing.[20]

Food allergy occurs in 6 to 8 percent of children 6 years of age or younger and in 2 percent of adults.[21] The prevalence in young children of allergy to cow's milk is 1.9 to 3.2 percent and to egg is 2.6 percent.[22] Other food allergens affect children and adults, including allergy to peanuts and tree nuts, which is estimated at 1 percent of the U.S. population.[23] These two foods are the leading causes of fatal and near-fatal food allergic reactions. About 30,000 Americans per year have anaphylaxis to food, and about 200 Americans, usually children, die annually from food-induced anaphylaxis.[21,24] Food allergy is the most frequent single cause of emergency room visits for anaphylaxis and accounts for 33 percent of such emergency room visits.[25-26]

In 1997, the National Health Interview Survey (NHIS) was redesigned to quantify active asthma among adults and children through diagnosis of asthma by a physician as well as an episode of asthma during the past year. Data from the NHIS indicate that approximately 11 million Americans had asthma in 1999, with an overall prevalence of 3.8 percent.[27] The economic costs of asthma continue to rise. In 1998, asthma accounted for an estimated $12.7 billion in expenditures, with $7.4 billion in direct medical expenditures and $5.3 billion in indirect costs.[28]

Asthma disproportionately affects children and minority populations, particularly African Americans. In 1999, asthma was more prevalent among African Americans (4.3 percent) than whites (3.8 percent), and this disparity was greater among children. Asthma was more prevalent among African-American children younger than 18 years of age than among white children of the same age (7.4 percent and 5.0 percent, respectively),[29] and this disparity was even greater for hospitalizations, emergency room visits, and deaths. African Americans were 3.4 times more likely than whites to be hospitalized for asthma. Emergency room visits for African Americans (174 per 10,000) were much more common than for whites (59 per 10,000). In 1999, 4,657 people died from asthma, or 1.7 per 100,000. The death rate among African Americans (3.9 per 100,000) was almost three times that among whites (1.4 per 100,000).[30]

The cause, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent major areas of emphasis for NIAID's Division of Allergy, Immunology and Transplantation (DAIT). NIAID vigorously pursues research on asthma and allergic diseases by fostering investigator-initiated projects and by supporting cooperative clinical studies, a national network of research centers, and demonstration and education research projects.

In the Inner-City Asthma Study (1996-2001), NIAID and the National Institute of Environmental Health Sciences (NIEHS) evaluated the effectiveness of two asthma interventions among children ages 5 to 11 with moderate to severe asthma. The physician feedback intervention provided primary care physicians with up-to-date information on recent asthma symptoms, medication, and health care utilization. The environmental intervention involved home-based education to reduce exposure to environmental triggers, including environmental tobacco smoke, cockroaches, house dust mites, molds, furry pets, and rodents. A total of 941 patients were recruited and evaluated for both the 1-year intervention period and an additional year of followup. Preliminary results suggest that the environmental intervention significantly reduced asthma morbidity and that the magnitude of reduction is correlated with the reduction in cockroach and house dust mite allergen levels. A substudy, funded jointly by NIAID, NIEHS, and the U.S. Environmental Protection Agency, evaluated the impact of fine particles and co-pollutants on respiratory morbidity. Analysis of data from the substudy is currently under way.

The NIAID Asthma and Allergic Diseases Research Centers program is the cornerstone of the pathobiology component of the Institute's asthma and allergy research program, providing support for basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of these diseases. In response to the recommendations of an expert panel convened in February 2000, the program requirements were revised to emphasize studies in humans. NIAID currently supports a national network of 13 Asthma and Allergic Diseases Research Centers, 2 of which are cofunded by NIEHS.

In 2001, NIAID collaborated with the Centers for Disease Control and Prevention to launch a program to disseminate and implement the very successful asthma intervention developed by the NIAID National Cooperative Inner-City Asthma Study (NCICAS, 1991-1996). This educational and behavioral intervention, delivered by an asthma counselor, has been shown to reduce symptoms and hospitalizations in inner-city children with moderate to severe asthma. NIAID-funded investigators translated the NCICAS research intervention into a form that can be efficiently used in a variety of health care delivery settings, including health maintenance organizations, health departments, and community clinics. The 4-year program targets children living in inner cities and is being implemented through 23 inner-city health care organizations throughout the United States. More than 6,000 inner-city children with asthma will benefit from the effort.

The Immune Tolerance Network (ITN), cofunded by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, is an international consortium of basic scientists and clinical investigators that performs clinical trials and mechanistic studies designed to evaluate the safety and efficacy of promising approaches to tolerance induction for

the treatment of immune-mediated disorders, including allergy and asthma. The ITN currently supports a trial of DNA-ragweed allergen conjugates for the treatment of allergic rhinitis. More information on the ITN is available on its Web site at *www.immunetolerance.org*.

An important NIAID intramural study is examining how allergen immunotherapy (AIT) works to reduce or prevent reactions to allergens such as pollen, dust, or cat dander. Although the efficacy of AIT in asthma is modest, it remains the only known disease-modifying therapy for allergic asthma. Certain types of white blood cells, called Th2 cells, produce substances that generate allergies, whereas others, called Th1 cells, produce substances that may inhibit the development of allergies. This study will determine whether AIT changes the immune response to allergens by reducing the number of Th2 cells or by converting them into Th1 cells. A better understanding of the mechanisms underlying the clinical effectiveness of AIT might help scientists to discover new approaches to treating allergies and asthma.

Scientific advances over the past several decades have revolutionized our understanding of the human immune system and have contributed significantly to extraordinary improvements in the treatment of many immune-mediated diseases. As the primary NIH Institute for research in immunology, NIAID has been at the forefront of many of these advances, including discoveries leading to the characterization of asthma and allergic diseases as immunologic disorders. With an enhanced understanding of the role of immune dysfunction in the pathogenesis of asthma and allergic diseases, NIAID is uniquely positioned to apply fundamental knowledge to develop novel therapies and eventually to prevent disease onset.

AUTOIMMUNE DISEASES

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. These diseases are a significant cause of chronic morbidity, costing billions of dollars annually in health care expenses and lost productivity. Autoimmune diseases can be divided into two main groups: organ-specific and non-organ-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Non-organ-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage.

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease.

Congressional interest in autoimmune diseases was expressed in both House and Senate FY 1998 Appropriations Committee Reports, encouraging the establishment of an NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC was established in June 1998 under the direction of NIAID. Committee members include representatives of 17 NIH Institutes, Centers, and Offices, the Food and Drug Administration, the Department of Veterans Affairs, the Centers for Disease Control and Prevention, and private organizations that support research in this area. The ADCC facilitates maximum coordination among groups working in areas of complementary and shared interests. As described in the Children's Health Act of 2000 (Public Law 106-310), in FY 2001, the ADCC began developing a strategic plan for research on the epidemiology and burden of disease; etiology and pathogenesis; diagnosis, treatment, and prevention; and training, education, and information dissemination. It is anticipated that this research plan will be presented to Congress in late 2002. The first report of the ADCC, published in December 2000, provides details on the individual initiatives, sponsors, and current and planned research on autoimmune diseases. The report is located at *www.niaid.nih.gov/dait/pdf/adccrev.pdf*.

DAIT supports several multicenter research programs on autoimmune diseases. The Autoimmunity Centers of Excellence (ACE) support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies. Clinical trials are under way for SLE, lupus nephritis, and multiple sclerosis. Protocols for clinical trials in type 1 diabetes are in development. In addition, several collaborations among ACE investigators will address the immune mechanisms underlying the agents evaluated in these trials.

In FY 1999, DAIT established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies in four clinical areas: autoimmune diseases, asthma and allergic diseases, and to prevent rejection of transplanted kidneys and pancreatic islets. The goal of these therapies is to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. An important aim of the ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate drugs. The ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. The ITN will perform clinical trials of promising tolerogenic approaches to prevent or treat multiple autoimmune diseases. These clinical trials include the following:

- The "Edmonton Protocol," an experimental islet transplantation protocol for patients with hard-to-control diabetes; and
- Clinical trials in development for multiple tolerance-induction approaches for multiple autoimmune diseases, including multiple sclerosis and type 1 diabetes.

The ITN is cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF). More information on the ITN is available on its Web site at *www.immunetolerance.org*.

NIAID has made awards under its Sex-Based Differences in the Immune Response Research Initiative. This program was established in FY 2001 to support basic and clinical research to identify, characterize, and define sex- and gender-based differences in the immune response.

An important new area of disease prevention focuses on the use of vaccination approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease exists, development appears to be feasible based on studies in animal models. The vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. The vaccines for autoimmune diseases will "turn off" a destructive immune response that is directed at the body's own tissues. NIAID, in collaboration with multiple NIH Institutes and the JDRF, awarded five cooperative agreements in FY 2001 to focus on development of the knowledge necessary to rationally design and implement strategies to prevent autoimmune diseases, including type 1 diabetes.

NIAID, in collaboration with NIDDK and the National Institute of Child Health and Human Development, supports the Diabetes Prevention Trial Type 1, a multisite cooperative clinical trial to test the efficacy of oral insulin to prevent type 1 diabetes in intermediate-risk populations. This is the first large nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. An arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which is testing the effectiveness of oral insulin to prevent the development of disease, is continuing to enroll participants. Through the ITN, Dr. Tihammer Orban is testing the safety of giving insulin B chain with adjuvant to individuals with new onset diabetes. If this approach proves safe without the induction of immunity to the insulin B chain, further studies

to test the ability of this combination to interrupt the autoimmune process in new onset or at risk individuals will follow.

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, DAIT is developing clinical trials to evaluate the safety and efficacy of hematopoietic stem cell transplantation as a treatment for several severe autoimmune diseases, including multiple sclerosis, SLE, and scleroderma.

DAIT supports two genetics research resources. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least two individuals are afflicted by two or more autoimmune diseases. The data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. More information can be found at *www.madgc.org.* DAIT, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation, supports the North American Rheumatoid Arthritis Consortium (NARAC). NARAC collects clinical data and genetic material from families with rheumatoid arthritis, which are made available to investigators to facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis. More information can be found at *http://narac.patternrx.com*.

NIAID, with cosponsorship from the National Cancer Institute, NIDDK, and the JDRF, continues to support the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that collects and shares data on genes of the human leukocyte antigen (HLA) complex. The IHWG will study five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy.

In addition, NIAID supports a project within the IHWG to discover single nucleotide polymorphisms (SNPs) in type-1-diabetes-related genes. SNPs are naturally occurring genetic variations that may affect the amount or function of the gene product. Once SNPs are identified, researchers will be able to analyze patient populations for the presence of these variations. The SNPs will be available in a public database to facilitate the search for susceptibility genes in subjects with type 1 diabetes.

Although we have gained considerable understanding of the immune mechanisms that mediate tissue injury in autoimmune diseases, much remains to be learned about the causes of these diseases, the underlying genetic susceptibility, the regulation of T-cell and autoantibody production, and the characterization of the cells and chemical mediators of inflammation. NIAID is committed to furthering the understanding of the immunopathogenesis of autoimmune diseases and to promoting the application of basic research to clinical investigations, which may result in the development of more effective therapeutic approaches and prevention strategies for these devastating diseases.

FINDING

Story of Discovery: Immune Therapy for Type 1 Diabetes

Type 1 diabetes is a chronic autoimmune disease that afflicts between 500,000 and one million people in the United States, usually children and young adults. Autoimmune diseases occur when the immune system attacks the body's own tissues. In type 1 diabetes, the immune system attacks and destroys the islet cells of the pancreas that secrete insulin, a hormone essential for the body's ability to use sugar from digested foods. The pancreas then produces little or no insulin, and patients must endure a difficult and life-long treatment regimen that includes multiple daily injections of insulin, multiple monitoring of blood glucose levels, and significant dietary requirements and restrictions. Furthermore, poor management of diabetes can lead to serious complications, such as blindness, kidney failure, heart disease, stroke, and foot and leg amputations.

Basic and Pre-Clinical Research: Putting the Pieces Together

Through years of research on the processes underlying autoimmune disorders, NIAID-supported scientists paved the way for the development of a new therapy for type 1 diabetes. When studies demonstrated that immune cells known as T cells were involved in the destruction of islet cells, researchers attempted to block the harmful actions of these cells with drugs that suppress the entire immune system. Unfortunately, the toxic side effects and increased risk of infection limited the use of these drugs. Developing a less toxic therapeutic approach that selectively blocks the harmful actions of the immune system while maintaining its ability to fight off infections would be a key step towards meeting the challenges posed by autoimmune reactions in type 1 diabetes. In the meantime, researchers working on novel immune therapies to prevent kidney transplant rejection developed an antibody against the CD3 complex, a cluster of molecules on the T cell surface that plays a central role in activating it to recognize and respond to toxins, bacteria, and other foreign cells. Graft rejection results when T cells recognize the transplanted organ as foreign and mount an attack against it. Studies with animal models of type 1 diabetes demonstrated that the anti-CD3 antibody could suppress the destructive T cells.

Transferring Findings to Patients

Based on the success of animal studies, NIH-supported researchers moved to test this approach in humans. They initiated a phase I trial to determine the safety of this anti-CD3 antibody in patients with new-onset type 1 diabetes. The researchers showed that administering this novel immunotherapy within 6 weeks of diagnosis of disease slowed down the loss of insulin production in 9 out of 12 young diabetic patients. The effects were still evident one year later, although the patients continued to require insulin therapy. The promising results of this preliminary study have led to a multi-center, phase II clinical trial, which is currently recruiting 80 additional patients between the ages of 7 and 27. The trial will be conducted by the Immune Tolerance Network

Story of Discovery: Immune Therapy for Type 1 Diabetes, Continued

under the co-sponsorship of NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International. Although this treatment is not a cure for type 1 diabetes, it brings us a step closer to the goal of preserving insulin production in people newly diagnosed with the disease. Greater ability to maintain the body's production of insulin will make it easier for the patients to control blood sugar levels, and improved metabolic control of diabetes will reduce the risk of developing diabetes-related complications. ❖

Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, and Bluestone JA: Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. New England Journal of Medicine 346: 1692-1698, 2002.

BIODEFENSE

A terrorist attack on the United States using biological agents, once thought to be a remote possibility, occurred in the fall of 2001 when *Bacillus anthrac*is spores were sent through the U.S. mail, causing 18 confirmed cases of anthrax (11 inhalation and 7 cutaneous). Recent events have raised awareness of both the possibility of a bioterrorist attack and the vulnerability of the U.S. population to such an event. Although other Government agencies have developed defenses for biological warfare, there are additional concerns that need to be addressed to provide an adequate civilian defense from a bioterrorist attack. First, the potential list of microbial pathogens that threaten civilian populations is larger than that of classical biological warfare threats. Moreover, the populations to be protected are different because civilians include people of all ages and physical conditions.

Our ability to detect and counter bioterrorism depends to a large degree on the state of biomedical science. Biodefense research supported by NIAID emphasizes four areas: basic research, new diagnostic tools, vaccines, and new treatments or therapeutics.

Basic Research

One of the most important basic research tools that has evolved in recent years is the ability to rapidly sequence the entire genomes of microbial pathogens, including potential agents of bioterrorism. This capability is important because when scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. In addition, because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins. Some agents, such as smallpox and other orthopoxviruses related to smallpox, have already been sequenced; the sequences of others are in progress. NIAID has recently expanded its sequencing efforts of *B. anthracis* to include more comprehensive genomic analysis. The fruits of this genomics research, coupled with other biochemical and microbiological information, are expected to facilitate the achievement of critical new goals, including the discovery of new targets for drugs and vaccines.

In addition, considerable knowledge about the mechanisms of host immune responses to microbial pathogens has been gained in recent years. Especially productive were studies on the constitutively present, innate immune mechanisms that serve as a first line of defense against pathogenic infection. For example, the identification and functional characterization of the Toll-like family of receptors expressed on cells of the human innate immune system has led to an explosion of information and innovative research activity now being applied to the development of new vaccine adjuvants and immunostimulatory agents to boost generalized immune protection. Additional progress on understanding the molecular mechanisms responsible for pathogen-specific, inducible immunity mediated by antibodies and cytotoxic T cells has led to new approaches in vaccine design. Furthermore, the threat of bioterrorism and the emergence of pathogens such as the West Nile virus have underscored the importance of defining the immune parameters responsible for the increased susceptibility of infants, young children, the elderly, and immunocompromised individuals to infectious disease.

New Diagnostic Tools

The NIH also supports research leading to the development of new and improved diagnostics. The goal of this research is to establish methods for the rapid, sensitive, and specific identification of natural and bioengineered microbes as well as the determination of the microbes' sensitivity to drug therapy. These scientific advances will allow health care workers to diagnose and treat patients more accurately and quickly.

Vaccines

NIH-supported researchers are developing vaccines that are effective against many infectious agents, including those considered to be bioterrorism threats, with the intention of developing products that are safe and effective in civilian populations of varying ages and health status. Vaccines against pathogens are being developed using both traditional and novel technologies. Some novel technologies include the development of DNA vaccines, various vector vaccines, and innovative systems for the rapid creation of vaccines against unfamiliar or genetically altered pathogens; these technologies are in various stages of development.

New Treatments or Therapeutics

NIH therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be used by bioterrorists. Knowledge gained from basic and applied research is helping to identify additional targets for medications and immune-based therapies against agents of bioterrorism.

In 2002, NIAID developed a strategic plan for biodefense research, which outlines plans for addressing research needs in the broad area of bioterrorism and emerging and re-emerging infectious diseases. In addition, NIAID convened a Blue Ribbon Panel of experts to provide objective scientific advice on NIAID's biodefense research agenda for Category A agents, which include major threats such as smallpox and anthrax. The experts were asked to assess the current research, identify goals for the highest priority areas, and make recommendations to achieve the goals. In fall 2002, NIAID convened another Blue Ribbon Panel of experts to similarly assess current research and identify goals for Category B and C agents.

In the last year, NIAID has markedly expanded, intensified, and accelerated its ongoing research programs in biodefense. NIAID has launched or expanded 35 research initiatives in areas ranging from the basic biology of microbes and their interactions with the human immune system to preclinical and clinical evaluation of new therapeutics and vaccines. These initiatives are designed to take advantage of the recent outpouring of ideas from academic and industrial scientists on ways to understand and combat potential agents of bioterrorism *(www.niaid.nih.gov/dmid/biodefense)*.

In addition, NIAID announced new initiatives for fiscal year 2003 to further expand biodefense research efforts. Several examples of these initiatives follow:

- **Development and Testing of Anthrax Recombinant Protective Antigen (rPA) Vaccine -** will provide resources for the advanced development and

production of a vaccine to protect the U.S population against inhalation anthrax when administered in an immunization series of not more than 3 doses.

- **Development and Testing of a Modified Vaccinia Virus Ankara (MVA) Vaccine**—will provide resources for the initial development of MVA vaccine candidates. The MVA vaccine is a second-generation smallpox vaccine made from a virus that has been further refined to limit its replication. The ultimate goal for NIAID is to develop a smallpox vaccine to protect all individuals regardless of their health status.

- **Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research**—will support large, multidisciplinary regional resources for the scientific community to provide the scientific information and translational research capacity to develop the next generation of therapeutics, vaccines, and diagnostics against Category A-C agents. The Regional Centers of Excellence will conduct multidisciplinary basic, translational, and clinical biodefense research, train new researchers for the field, and serve as regional focal points for biodefense activities.

- **Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, and Diagnostics for Biodefense**—will establish a translational research program to develop an increased understanding of the mechanisms of pathogenesis, epidemiology, natural history, and ecology of the CDC Category A-C biological diseases/agents to facilitate the subsequent design and development of interventions and diagnostics.

- **Partnerships for Biodefense**—will support work on new drug development and on faster, more accurate diagnostics for diseases of public health importance, including those caused by possible agents of bioterrorism. This program seeks to foster partnerships among Government, academia, and the biotechnology and pharmaceutical industries. It builds on an established program that supports research on infectious diseases that are not a high priority for industry.

- **Small Business Biodefense Program**—will encourage the development of therapeutics, vaccines, adjuvants/immunostimulants, diagnostics, and selected resources for biodefense by the small business research community. This program expands duration and dollar limits for small business grants to develop specified products that are considered high priority for biodefense.

- **Cooperative Centers for Traditional Research on Human Immunology and Biodefense**—will fund new multidisciplinary grants to facilitate the translation of research in animal models, such as the mouse, into studies in the human. New technologies will be developed to allow more definitive studies of human immune responses and regulation, and research on human immunity to NIAID Category A-C priority pathogens will be conducted to support improved vaccine designs and the development of novel immunotherapeutic agents.

- **Large-Scale Antibody and T-Cell Epitope Discovery and Database Programs**—are designed to support the rapid identification and verification of the regions on pathogens, called epitopes, that are recognized by specific antibodies or cytotoxic T cells to mediate elimination of the pathogen. In addition to the discovery research program, a comprehensive centralized database will be established to provide a Web-based searchable source of information on pathogen epitopes for researchers. Included in the database is an analysis resource to facilitate data analysis and predict epitopes from new pathogens.

- **Hyperaccelerated Award/Mechanisms in Immunomodulation Trials**—will fund immunologic studies that accompany clinical trials of vaccines against Category A-C pathogens. This program will provide rapid support for sophisticated laboratory studies defining the immunologic mechanisms of protection of successful new vaccine candidates, or defining reasons for failure of vaccine candidates and targets for improvement.

Because smallpox was eradicated as a natural disease in 1980, general vaccination was discontinued and no new vaccine stocks were produced. In response to concerns about the limited stock of smallpox vaccine, NIAID accelerated the design and implementation of a large multisite study to determine the feasibility of diluting the existing Dryvax vaccine. The study compared the effectiveness of full-strength smallpox vaccine with that of fivefold and tenfold diluted vaccine in 679 adults aged 18 to 32 with no history of smallpox vaccination. More than 97 percent of all participants in the study responded with a vaccine "take," a blister-like sore at the injection site that serves as an indirect measure of the vaccine's effectiveness. Most important, the investigators found no significant difference in the take rate of the three doses. The study was conducted at several NIAID Vaccine and Treatment Evaluation Units around the United States, including St. Louis University, Baylor College of Medicine, the University of Maryland, and the University of Rochester.[31]

NIAID Intramural Research Programs

NIAID's intramural laboratories are conducting many new and ongoing projects to address gaps in our knowledge of select agents, including basic studies of organism biology and disease mechanisms, studies of host response to infection, and development of vaccines and therapeutics. Many of these projects include collaborators from academia, other Government agencies including the military, and private industry. Efforts also are under way to improve NIAID's research infrastructure to ensure our facilities can safely accommodate our planned work with select agents and emerging diseases as well as provide the flexibility necessary to be prepared for future needs.

Biology of the Microbe

NIAID has a longstanding intramural research program aimed at shedding light on the molecular biology and gene expression mechanisms used by vaccinia—the virus used in the current smallpox vaccine—and other poxviruses. For example, NIAID intramural investigators and their collaborators determined the genetic relationship between variola—the smallpox virus,—and monkeypox virus, which causes a human disease resembling smallpox but with a lower person-to-person transmission rate. They found that the region of the monkeypox genome that encodes essential enzymes and structural proteins was 96.3

percent identical to that of smallpox; however, genes encoding virulence and host-range factors were considerably different, indicating that monkeypox is not the direct ancestor of smallpox and is unlikely to naturally acquire all properties of smallpox.[32] This program has increased our understanding of poxviruses and facilitated the construction of improved vaccinia expression vectors for vaccines and gene therapy.

NIAID intramural investigations of plague have resulted in the development of a system to study the fundamental biology of the interaction between *Yersinia pestis*—the bacterium that causes plague—and its flea vector. Using this system, NIAID scientists discovered that a single gene change allowed *Y. pestis* to survive in the flea midgut and thus evolve from a form that caused only a mild intestinal illness, acquired through ingestion, to become a much more deadly infection transmitted by fleas.[33] This work will further efforts to design strategies to disrupt plague transmission cycles. NIAID plague investigators also established mouse and rat models of bubonic plague that incorporate the natural fleaborne route of transmission for studies of plague pathogenesis. The mouse model will be used to evaluate a new recombinant vaccine developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) for its ability to protect mice against fleaborne transmission of *Y. pestis*.

Intramural studies of *B. anthracis*, the etiologic agent of anthrax, are focused on identification and analysis of bacterial virulence factors and their genetic regulation, structure-function analysis of bacterial toxin proteins and other virulence factors, and development of improved vaccines and therapeutics. NIAID is expanding intramural studies of the action of the anthrax toxin to appropriate small animal models to determine the molecular targets of anthrax toxin and identify opportunities for specific therapy of anthrax infections.

Additional work under way in NIAID laboratories includes investigation of highly virulent group A streptococcus to understand the mechanisms by which organisms become more virulent; studies of the pathogenesis of *Coxiella burnetti*, the agent of Q fever; studies of multi-drug-resistant tuberculosis; and studies of relapsing fever agents, with a focus on improving the laboratory tests to detect infection.

Vaccines

To address the need for a safer smallpox vaccine, NIAID experts in viral immunology and cell biology are teaming with private industry to develop a new, noninfectious smallpox vaccine. The collaborators will study recipients of smallpox vaccine (vaccinia virus) to define the specific parts of the vaccine that are most important for eliciting cross-reactive immunity to smallpox. Ultimately, they will combine these noninfectious pieces of virus in an optimized, noninfectious vaccine for conducting challenge trials with vaccinia virus. Successful trials with vaccinia virus would strongly suggest protection against infection with the smallpox virus. In addition, researchers at the Vaccine Research Center (VRC) are working with others at NIAID to explore the use of a replication-defective vaccinia virus, modified vaccinia virus Ankara (or MVA), as a potential component of a safer smallpox vaccine.

Another longstanding NIAID intramural research program focused on studies of the tickborne flavivirus complex has ramped up

efforts to develop a vaccine against tickborne encephalitis virus and other highly virulent members of this group, which includes the hemorrhagic fever viruses Kyasanur forest disease virus and Omsk hemorrhagic fever virus. These viruses, along with a nonvirulent member called Langat virus, share components that can induce cross-resistance among other members of the group. In a collaborative effort with USAMRIID colleagues, NIAID scientists are refining an approach they devised nearly 10 years ago that uses a chimeric live virus—composed of parts of different flaviviruses—for the candidate vaccine. This approach allows the scientists to significantly weaken the vaccine candidate while maintaining the advantages of a live vaccine in inducing a strong protective immune response.[34] This strategy also has been applied to construct a vaccine against West Nile virus.

Hemorrhagic fevers, such as Ebola, are associated with a high mortality rate, particularly for the Ebola Zaire subtype. Traditional public health measures to prevent future outbreaks are limited, thus increasing the urgency for development of an effective vaccine. Previously, it had been shown that immunization with DNA-encoding Zaire-subtype glycoprotein (GP[Z]) yielded a significant humoral protective response in guinea pigs. The VRC carried out additional studies and determined that a prime-boost strategy, with naked DNA as prime (initiation of an immune response) and recombinant adenoviral vector as boost (enhancement of the initial immune response) substantially enhanced the immune response. The VRC will continue to develop and test multivalent vaccines to evaluate their protection against multiple hemorrhagic fever pathogens of natural or deliberate infections.

Therapeutics

NIAID clinical investigators have an approved protocol in place that will allow them to evaluate and treat persons with suspected exposure to or infection with anthrax and to conduct immunologic evaluations of anthrax vaccines. A vaccinia clinical protocol is under development. These protocols also will allow investigators to determine the parameters of the host immune response to anthrax and vaccinia immunization and to anthrax exposure or infection.

NIAID scientists also are working to improve the production and efficacy of immune globulins for prophylaxis or therapy for anthrax and smallpox infection. Immune globulins are protective antibodies produced by the host in response to infection or immunization. NIAID investigators have immunized a group of chimpanzees with smallpox vaccine and have begun to generate specific neutralizing antibodies to vaccine components. Later, they will test these antibodies for efficacy *in vitro* and *in vivo*. A second group of animals is being readied for immunization with anthrax toxin.

BIOENGINEERING, BIOINFORMATICS, AND OTHER EMERGING TECHNOLOGIES

Bioengineering, bioinformatics, and other emerging technologies are crosscutting tools to facilitate research in many disciplines. Bioengineering combines physics, chemistry, and mathematics as well as basic engineering principles to enhance the study of biology, medicine, behavior, and health. Bioinformatics and computational biology involve the application of computer science and advanced mathematics to enable integration and analyses of biological, medical, behavioral, and health data.

The unique tools and approaches of bioengineering, bioinformatics, and computational biology are becoming integral components of NIAID-supported basic and clinical immunology research, and extend the capacity of science to perceive, capture, and manage information about biological processes. Recent innovations in the emerging fields of proteomics, sensors, and data integration promise to develop this infrastructure even further and yield real benefits for researchers in the near future. Each of the examples below illustrates the interdependence between the basic sciences, medicine, and the computer and engineering sciences.

- **Mass spectrometry for high-throughput peptide characterization**. NIAID-funded investigators are developing chemical measurement instruments for the sequence analysis of peptide antigens presented in the major histocompatibility complex. This research will lead to a high-throughput method to study peptides that are recognized by the body as "self." Understanding how the body distinguishes itself from foreign (possibly harmful) agents is relevant to all immune-mediated diseases.

- **Biosensors for investigating the developing immune system**. A multidisciplinary team of NIAID-supported investigators is utilizing sensitive miniaturized sensors to detect and quantify immune responses in real-time. The program focuses on the development of B-cell function during an immune response by characterizing the production of antibodies and specific growth factors produced by the B cells and other immune cells.

- **Translational bioinformatics based on sexually transmitted pathogens**. NIAID supports databases of genomic information, as well as analysis tools for the multidisciplinary study of sexually transmitted pathogens. (See *www.stdgen.lanl.gov* and *www.poxvirus.org.*) This work involves the curation of molecular information pertaining to sexually transmitted bacteria and viruses, including pneumoniae, chlamydia, papillomavirus, herpes, and gonorrheae, and extending far beyond molecular sequence data. This resource is curated by the Los Alamos National Laboratory and is also supported by the U.S. Department of Defense.

- **Modular gene assembly**. A new system is being developed for engineering genes on the basis of their binding and activation properties, as well as their diverse features. This research will enable the formation, selection, and assembly of genes based on individual functional traits, which may lead to the development of novel therapeutic compounds, such as custom antibodies or immunosuppressants.

- **Drug discovery by high-throughput screening methods**. The goal of this project is to identify anti-inflammatory and immunosuppressive agents that are agonists for specific cellular receptors. The system is set up to analyze up to 1,000 samples simultaneously and uses bioinformatic analysis and computational models to aid in drug discovery.

- **Microchip drug delivery system.** NIAID-funded investigators are developing a novel drug delivery device (silicon-based microchips) that is capable of delivering a complex regimen of bioactive agents to a specific organ or tissue. The investigators have shown that a silicon-based microchip device, with no moving parts, can be operated *in vivo*. Controlled delivery has the advantage of providing a concentrated amount of drug or bioactive compound to the affected tissue, bypassing possible toxic side effects or inefficient delivery of systemically administered compounds.

- **Whole-organism imaging of immune response**. The ability to monitor the precise ways in which T cells accumulate in lymphoid organs, such as the liver, kidney, and bowel, or in the central nervous system holds important keys to understanding immune responses to pathogens and immune-mediated diseases. For example, the monitoring of cell migration can provide an early warning of acute graft rejection in organ transplant recipients. NIAID-funded investigators are applying imaging technologies to detect the accumulation of labeled T cells and macrophages in organ transplants, as well as to examine the development of systemic autoimmunity *in vivo*. Another NIAID-funded project is developing new magnetic resonance imaging analysis to track immune responses *in vivo*.

- **Bioinformatics infrastructure for scientific data sharing**. The rapidly emerging field of proteomics will provide a wealth of information about the characteristics of each protein, including function, structure, location, variants, and similarities to other proteins. NIAID supports efforts to develop new tools to monitor and manipulate gene expression. In FY 2002, NIAID established the Bioinformatics Integration Support Contract (BISC) to (1) link genomic and other basic scientific and clinical data from a variety of sources, (2) enable scientists to easily access, generate, and exchange complex, high-quality data sets, and (3) serve the data integration and archiving needs of several large research programs supported by NIAID.

DRUG RESEARCH AND DEVELOPMENT

The development of therapies to treat infectious and immune-mediated diseases is a key component of NIAID's mission. Basic research serves as the foundation for drug development through scientific advances in microbiology, virology, and immunology. Advances in these areas help to identify potential targets for therapeutic agents and potential strategies for treating infectious and immune-mediated diseases. Through collaborations with industry, academia, and other Government agencies, NIAID has established research programs to facilitate drug development, including databases of chemical structures and chemicals that can be screened for potential use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trials networks to evaluate the safety and efficacy of drugs and therapeutic strategies.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes substantial resources to the discovery and development of new therapeutics for HIV/AIDS as well as AIDS-associated opportunistic infections, co-infections, and malignancies, attempting to focus resources on areas of promise that receive insufficient support elsewhere. A strong portfolio of basic research serves as the foundation for these activities.

Over the past 13 years, drug discovery efforts have concentrated on a relatively small number of viral targets: reverse transcriptase (RT), the enzyme that catalyzes the synthesis of viral DNA from the RNA template present in the incoming, or infecting virion, and protease (PR), the enzyme that affects HIV maturation by cleaving and processing viral precursor proteins to their mature form. The combined use of RT and PR inhibitors (known as highly active antiretroviral therapy, or HAART) has been successful in suppressing HIV and decreasing the incidence of opportunistic infections. Nonetheless, complications have emerged with these antiviral agents, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by HAART. Recently, new classes of therapeutic agents have entered the development pipeline. These include agents that interfere with virus binding and entry into the cell as well as therapeutics directed at other viral targets, such as HIV integrase, which is used by HIV to incorporate its genetic material into a host cell's DNA. Inhibition of HIV integrase is an attractive therapeutic strategy because it would potentially protect healthy cells from infection, thereby helping to bolster the immune system. In addition, therapeutic vaccines represent a potential new immunologic approach to complement drug treatment. Thus, while advances continue to be made, there remains an urgent need for the identification of new host and viral targets, novel drugs and delivery systems, and immunologic approaches to address the dual problems of drug resistance and toxicity.

HIV therapeutics are discovered through a number of approaches, beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle, immunopathogenic studies to further understand the nature of HIV-mediated immune deficiency, genetic studies to define genes responsible for control of transmission susceptibility and disease progression, and

strategies to restore or reconstitute effective immune function. The approaches are the foundation for targeted drug discovery, pursued through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Current programs targeting therapeutics research on HIV/AIDS, its complications, and co-infections include the Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP); HIV Therapeutics: Targeting Research Gaps Program; Innovation Grants for AIDS Research Program; Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; and Liver and Pancreatic Disease in HIV Infection Program.

The IPCP supports the discovery, preclinical evaluation, development, and pilot clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is discovered, development proceeds through additional *in vitro* testing. Additional information is obtained by evaluating the agent's activity against a range of HIV isolates, testing in animal models of HIV infection, when appropriate, assessing the toxicity in different cell lines and animal models, and conducting pharmacologic studies. If appropriate, the IPCP supports early clinical evaluation in human studies.

The HIV Therapeutics: Targeting Research Gaps Program supports applied studies in specific gap areas identified in HIV therapeutics, including (1) discovery and validation of new viral and cellular targets, (2) innate immunity as it relates to susceptibility to HIV infection, disease progression, and new therapeutic strategies, (3) identification of agents/strategies for targeting and eliminating HIV reservoirs, and (4) design and development of therapeutic concepts to address immune deficits of HIV-infected individuals. Research supported by this program is expected to provide new viral and cellular drug targets, HIV inhibitors, and treatment concepts and ultimately result in the expansion of the HIV therapeutics research and development pipeline.

The Innovation Grants for AIDS Research Program supports research ideas that are novel, innovative, or in the early stages of development, with the expectation that innovative research in these fields will affect understanding of the HIV pathogenesis and disease progression and provide new concepts for prevention and therapy. Targeted research for this program includes (1) therapeutic discoveries, (2) microbicide discovery, and (3) HIV pathogenesis.

The Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program is intended to stimulate iterative preclinical research for novel therapeutic strategies against opportunistic infections, co-infections, and malignancies in people with HIV/AIDS. This program is sponsored jointly with the National Cancer Institute and the National Institute of Dental and Craniofacial Research. The AIDS-associated infections emphasized by this program are *Mycobacterium tuberculosis, Pneumocystis carinii, Cryptosporidium parvum*, and the microsporidia. The AIDS-associated malignancies emphasized by this program are Kaposi's sarcoma, lymphomas, cervical cancer, oral warts and cancers, and anogenital cancers.

The Liver and Pancreatic Disease in HIV Infection Program is intended to stimulate research on the pathogenesis and therapeutics of the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. This program is sponsored jointly with the National Institute of Diabetes and Digestive and Kidney Diseases. The co-infections emphasized by this program include hepatitis B and hepatitis C. Metabolic complications include hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis, and pancreatitis.

Contract resources are also devoted to supporting clinical research on therapeutic interventions for *Mycobacterium tuberculosis* (Mtb) infection and co-infection with HIV *(www.taacf.org)*. These interventions include high-throughput screening of anti-Mtb compounds and testing in animal models. For more information on research on Mtb, please see the section on tuberculosis on page 79.

Another important element of the DAIDS therapeutics discovery and development effort is the acquisition and dissemination of information on agents or strategies that show potential for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also conducts a program of surveillance by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff members use these databases to monitor compounds already under investigation and to identify additional entities to be pursued. Information from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS conducts clinical trials to examine its effectiveness in improving the quality and duration of life for HIV-infected individuals. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). These programs investigate therapeutic agents and novel treatment approaches, including studies to evaluate safety, dose, activity, efficacy, and optimal use. Together, they represent the largest AIDS clinical trials network in the United States and probably in the world.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports research to facilitate the discovery and evaluation of new drugs for infectious diseases. This research is supported at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Current drug development efforts address a wide spectrum of infectious agents, including hepatitis, herpes, tuberculosis (TB), sexually transmitted diseases (STDs), malaria, fungal diseases, viral respiratory infections, and pneumonia.

The drug research and development efforts of DMID reflect the Division's broad purview and accordingly encompass a diverse range of target organisms and treatment strategies. The activities support all stages of drug discovery and development, from the test tube to the bedside, and, especially for animal model and clinical research, involve close collaborations with colleagues from the pharmaceutical industry and the Food and Drug Administration (FDA).

DMID also supports more than 40 large-scale genome-sequencing projects; this information has the potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

Discovery and Preclinical Evaluation

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against hepatitis B virus (HBV), hepatitis C virus (HCV), influenza, respiratory syncytial virus (RSV), cytomegalovirus (CMV), vaccinia, and other viruses that cause hemorrhagic fevers and encephalitides, including West Nile virus. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts.

DMID supports investigators conducting basic and applied research on the discovery and design of antiviral agents. These projects have led to the design of new drugs for influenza, CMV, poxvirus, and hepatitis infections. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. Recent studies have included demonstration of the superiority of the combination of acyclovir and the herpes simplex virus-specific antibody over either agent alone as a therapy for the mouse equivalent of neonatal herpes, and the development of a hamster model of West Nile virus encephalitis that will provide an inexpensive, readily available means to test potential therapies. Other recent findings have identified several drugs with activity against members of the poxvirus family, which might be helpful in the event of a bioterrorist attack using smallpox.

Basic research on microbe replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites and of strategies to develop new agents based on this knowledge. For example, research projects on malaria include identification and characterization of unique parasite biochemical pathways that may serve as targets for drugs, determination of the mode of action of existing and potential drugs, and analysis of the mechanisms by which the parasite has become resistant to existing drugs.

An increasingly important contributor to the emergence of many infectious diseases, including pneumonia and TB, is the emergence of drug-resistant pathogens. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. This situation is becoming an increasingly important public health concern. In response, the Public Health Service, under the leadership of the NIH, the FDA, and the Centers for Disease Control and Prevention, has developed an antimicrobial resistance plan that provides a blueprint for specific coordinated Federal actions to address the emerging threat of antimicrobial resistance. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) production development. NIAID has the lead in the area of research. *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues* is available online at *www.cdc.gov/drugresistance*.

Clinical Studies

DMID clinical research is supported either by individual grants or by contract-supported programs, such as the Collaborative Antiviral Study Group (CASG) and the Bacteriology and

Mycology Study Group (BAMSG). The CASG is supported by a single award to the University of Alabama at Birmingham and by subcontracts to more than 100 collaborating sites. The CASG has recently established the safety and effectiveness of a new dose of the standard antiviral drug acyclovir, advancing the treatment of neonatal herpes virus infections. In addition, the CASG has demonstrated that an anti-CMV drug can decrease hearing loss in infants with symptomatic congenital ear infection. Currently, the CASG is evaluating new therapies for congenital CMV, herpes simplex encephalitis, RSV, and HCV infections. Studies of experimental therapies for West Nile encephalitis are in the planning stages.

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, supported clinical trials examining antifungal therapy in the opportunistic and endemic mycoses (fungal infections) since the first study done in the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two new contracts were awarded: BAMSG and Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU). BAMSG conducts clinical trials for evaluating interventions for serious fungal diseases as well as health-care-associated resistant bacterial infections. BAMBU provides biostatistical and administrative support for these clinical trials.

A phase I study evaluating a new monoclonal antibody treatment in patients who have recovered from AIDS-associated cryptococcal meningitis was completed recently under the MSG and BAMSG contracts. New clinical trials in development include the following treatments: antifungal drugs and immune-based therapeutics, combination antifungal drugs for life-threatening fungal infections, and infection control strategies to reduce colonization and infection caused by multi-drug-resistant bacteria in intensive care unit settings.

Other DMID-supported research groups that conduct drug evaluations as a part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases Cooperative Research Centers, and the Sexually Transmitted Diseases Clinical Trials Unit. In 2000, NIAID launched a phase III efficacy trial, Azithromycin Versus Benzathine Penicillin for the Treatment of Early Syphilis, through its STD Clinical Trials Unit. This trial is open to enrollment in the United States and Madagascar. The purpose of this study is to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment. In addition, single-project grants and contracts also support therapeutic evaluations for a number of diseases.

Treatment-Related Research

The first step toward appropriate treatment of an infectious disease is the availability of a sensitive and specific diagnostic reagent. DMID supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. For example, DMID supports the development and manufacture of rapid, inexpensive diagnostic tests for STDs. The Division also supports research focused on the development of topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent sexually transmitted infections.

In September 2000, NIAID convened, with industry, the Summit on Development of Infectious Disease Therapeutics to discuss the state of development of new therapeutics for

infectious diseases, including ways in which NIAID could better assist industry and academia in antimicrobial drug development for public health needs. On the basis of recommendations from this meeting, NIAID developed a research initiative titled Partnerships for Novel Therapeutic, Diagnostic, and Vector Control Strategies in Infectious Diseases to support the development of drugs and diagnostics for human infectious diseases of public health importance and products for controlling insects and other organisms that transmit infectious agents. A key component of this initiative is the development of appropriate partnerships among Government, academia, and the biotechnology, chemical, and pharmaceutical industries.

Division of Allergy, Immunology and Transplantation

The Division of Allergy, Immunology and Transplantation (DAIT) supports the research and development of drugs and biologics to treat and prevent immune-mediated diseases. Areas of research include therapeutic approaches to autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues, including bone marrow. DAIT established collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials. DAIT-supported researchers are investigating ways to transfer genes that encode the immunotherapeutic molecules into lymphocytes or mucosal membranes for delivery to the patient.

Several investigations are under way to evaluate new and potentially more effective therapies for asthma and allergic diseases, including multiple approaches to immunization and development of new agonist or antagonist medications. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to prevent and treat autoimmune diseases. These centers encompass expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel diseases, and type 1 diabetes.

DAIT Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation are evaluating a variety of therapies to improve graft survival and to prevent acute and chronic graft rejection. New approaches and therapeutic agents under investigation include monoclonal antibodies in conjunction with standard immunosuppressive therapy, new immunosuppressive drugs to prevent and reverse chronic rejection, pretransplant induction therapies to decrease acute graft rejection and to prevent the onset of chronic rejection, and intravenous gamma globulin to reduce high levels of sensitization among some end-stage renal disease patients, thereby enabling them to become candidates for transplantation.

DAIT, with cosponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, continues to support the Immune Tolerance Network (ITN). In FY 1999, DAIT established the ITN, an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies in the following clinical areas: autoimmune diseases, asthma and allergic diseases, and to prevent rejection of transplanted kidneys and pancreatic islets. The goal of tolerance-inducing therapies is to reeducate the immune system to eliminate injurious immune responses and graft rejection

while preserving protective immunity to infectious agents. An important aim of the ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate drugs. The ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia.

Division of Intramural Research

Much of the research under way in NIAID's Division of Intramural Research (DIR) is aimed ultimately at the development of more effective therapies for infectious and immunologic diseases. The DIR's basic studies of the immune system, disease pathogenesis, and microorganism structure, replication, and transmission often reveal potential new therapeutic targets for treating immunologic and infectious diseases. In addition, new technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. For example:

- DIR scientists are studying the basic mechanisms underlying the effectiveness of current TB medications and integrating genomics and combinatorial chemistry to hone development of second-generation therapeutics based on the same mode of action.
- Studies of mast cells, which initiate and perpetuate allergic inflammation, are identifying key biologic steps in the control of mast cell number and function to identify new approaches, such as cytokine-based therapies, to treat allergic inflammatory diseases.
- DIR investigations of the pathogenesis of prion proteins have identified compounds that inhibit the formation of the abnormal prion protein associated with the transmissible spongiform encephalopathies, often fatal neurologic diseases affecting animals and humans. These compounds are being tested in rodent models.
- NIAID AIDS researchers have designed a new recombinant protein that inhibits HIV binding to the CD4 receptor. The new protein has been engineered to address the shortcomings of an earlier viral entry inhibitor called soluble CD4, one of the first anti-HIV-1 therapeutics to be tested clinically, which failed to demonstrate clinical efficacy. The new protein appears to have the biochemical properties necessary for efficient inhibition of viral entry and will be tested soon in an animal model.

In addition to these examples of studies under way in the laboratories, DIR scientists are conducting more than 80 clinical research protocols at the Warren Grant Magnuson Clinical Center on the NIH campus. Many of these protocols are testing the efficacy of new drug therapies developed in DIR laboratories.

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

New infectious diseases continue to "emerge." Within the past two decades, improved diagnostic and detection methods have revealed a number of previously unknown human pathogens. (For a list of emerging and re-emerging diseases and pathogens, see the table below or *www.niaid.nih.gov/dmid/eid/erd.htm*.)

Largely as a result of better detection methods, evidence also is accumulating that infective agents play a role in diseases previously thought to be chronic and noncommunicable. In addition, changes in human demographics, behavior, and land use are all contributing to changing transmission dynamics by bringing people into closer and more frequent contact with pathogens. This situation may involve exposure to animal or arthropod carriers of disease. For example, transmissible spongiform encephalopathy (TSE) involves the transmission of disease from animals to humans through newly identified agents called prions.

In addition to the continual discovery of new human pathogens, old infectious disease enemies are "re-emerging." Natural genetic variations, recombinations, and adaptations allow new strains of pathogens to appear. The immune system has not been previously exposed to these pathogens and therefore is not primed to recognize them (e.g., influenza). Furthermore, human intervention plays a big role in reemergence. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistance, allowing many diseases to make a comeback (e.g., tuberculosis [TB], malaria, nosocomial [hospital-acquired], and foodborne infections).

List of NIAID Emerging and Re-emerging Diseases 2002

Group I—Pathogens Newly Recognized in the Past Two Decades

Acanthamebiasis
Australian bat *Lyssavirus*
Babesia, atypical
Bartonella henselae
Cyclospora cayetanensis
Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
Hendra or equine morbilli virus
Hepatitis C
Hepatitis E
Human herpesvirus 8
Human herpesvirus 6
Lyme borreliosis
Microsporidia
Parvovirus B19

Group II—Re-emerging Pathogens

Coccidioides immitis
Enterovirus 71
Prion diseases
Streptococcus, group A
Staphylococcus aureus

⇨

List of NIAID Emerging and Re-emerging Diseases 2002, Continued

Group III—Agents With Bioterrorism Potential

CDC—Category A

Bacillus anthracis (anthrax)
Clostridium botulinum
Francisella tularensis (tularemia)
Variola major (smallpox) and other pox viruses
Viral hemorrhagic fevers
- Arenaviruses
- Dengue
- Ebola
- Hantaviruses causing Hantavirus Pulmonary Syndrome
- Lassa fever
- LCM, Junin virus, Machupo virus, Guanarito virus
- Marburg virus
- Rift Valley fever

Yersinia pestis

CDC—Category B

Brucella species (brucellosis)
Burkholderia mallei (glanders)
Coxiella burnetti (Q fever)
Epsilon toxin of *Clostridium perfringens*
Foodborne and Waterborne Pathogens
- Bacteria
  - *Campylobacter jejuni*
  - Diarrheagenic *E. coli*
  - *Listeria monocytogenes*
  - Pathogenic vibrios
  - *Salmonella*
  - *Shigella* species
  - *Yersinia enterocolitica*
- Protozoa
  - *Cryptosporidium parvum*
  - *Cyclospora cayatanensis*
- Protozoa Continued
  - *Entamoeba histolytica*
  - *Giardia lamblia*
  - Microsporidia
  - Toxoplasma
- Viruses (calciviruses, hepatitis A)
- Additional viral encephalitides
  - California encephalitis
  - EEE
  - Japanese encephalitis virus
  - Kysanur Forest virus
  - LaCrosse virus
  - VEE
  - WEE
  - West Nile virus

Ricin toxin (from *Ricinus communis*)
Staphylococcal enterotoxin B
Typhus fever (*Rickettsia prowazekii*)

CDC—Category C

Emerging infectious disease threats, such as Nipah virus, additional hantaviruses, and the following pathogens:
- Influenza
  - Other rickettsias
- Multi-drug-resistant TB
- Rabies
- Tickborne encephalitis viruses
- Tickborne hemorrhagic fever viruses
  - Crimean-Congo hemorrhagic fever virus
- Yellow fever

Pathogens that naturally emerge with, or are engineered for, increased virulence, increased transmission, and/or the ability to evade the immune response. ❖

The use of deadly pathogens, such as smallpox or anthrax, as agents of bioterrorism is an increasingly acknowledged threat to the civilian population. Moreover, many important infectious diseases have never been adequately controlled on either the national or international level. Infectious diseases that have posed ongoing health problems in developing countries are re-emerging in the United States—for example, foodborne and water-borne infections, dengue, and West Nile virus.

In response to the threat of emerging and re-emerging infectious diseases, NIAID has developed a strategy for addressing these issues through targeted research and training. That strategy, which was initially outlined in the Institute's 1996 document, *A Research Agenda for Emerging Infectious Diseases (www.niaid.nih.gov/publications/execsum/bookcover.htm)*, was updated in the recent NIAID strategic plan, *NIAID: Planning for the 21st Century (www.niaid.nih.gov/strategicplan/pdf/splan.pdf)*. In May 2001, NIAID released the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis* (*www.niaid.nih.gov/publications/globalhealth/global.pdf*). This document outlines the Institute's plans for the next decade for diagnosing, treating, and preventing these three infections and also lays out a plan for enhancing in-country research capacity.

To an unprecedented extent, issues related to infectious diseases in the context of global health are on the agendas of world leaders, health policymakers, and philanthropies. This attention has been focused both on scientific challenges, such as vaccine development, and on the deleterious effects of infectious diseases on economic development and political stability.

To enhance the capacity to deal with the challenges posed by emerging diseases, NIAID has constructed a new biosafety-level-three (BSL-3) laboratory in Hamilton, Montana, and is in the process of constructing a BSL-3 laboratory in Rockville, Maryland. NIAID also is developing plans for a BSL-3 laboratory in the Bethesda, Maryland, area. These laboratories will enable the Institute to conduct BSL-3 animal studies and laboratory research on infectious agents, such as multi-drug-resistant *Mycobacterium tuberculosis* (Mtb). Research programs on pathogenic microorganisms, including *Borrelia*, *Yersinia*, the influenza virus, West Nile virus, and dengue virus, will be continued and expanded.

Basic and clinical research is critical to the development of a national strategy to confront these microbial challenges. Such research increases our collective understanding of ever-changing microbial populations and permits this new knowledge to be transformed into better diagnostics, vaccines, and therapies. Basic research and research training also are the foundation for surveillance and response activities.

During 2002, NIAID supported research initiatives on biodefense as well as on emerging and re-emerging infectious diseases in multiple areas, including TB, Lyme disease, influenza, prion diseases, and other infectious diseases and deadly pathogens.

Biodefense Research

NIAID continues to expand its research related to potential agents of bioterrorism. In spring 2002, NIAID released the *NIAID Biodefense Research Agenda for CDC Category A Agents*, a document describing the Institute's accelerated research plan for the most threatening agents of bioterrorism. The agenda

outlines the research NIAID will undertake to help protect civilian populations from diseases such as smallpox, anthrax, and plague should they be unleashed intentionally by those who wish to do harm. The comprehensive plan includes short-, intermediate-, and long-term research goals and describes specifically how bioterrorism countermeasures will be developed for each microbe. The document also contains a copy of the *NIAID Strategic Plan for Biodefense Research*, which provides a general overview of the Institute's broad plans for attacking the full range of potential bioterrorism pathogens. The research agenda can be found at *www.niaid.nih.gov/biodefense/research/biotresearchagenda.pdf.*

See page 60 for more information on NIAID biodefense research.

Emerging and Re-emerging Infectious Diseases

West Nile Virus

NIAID supports a robust West Nile virus research portfolio. The following points summarize key research in several different areas:

- Basic research leads to a better understanding of the host, pathogen, and environmental factors that influence disease emergence. Basic research determines which flavivirus proteins contribute to the virus's ability to cause disease and examines how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis.
- A golden hamster model has been developed by NIAID-supported researchers and is used for screening drugs and for examining factors that contribute to immunity. This model has proven useful in evaluating strategies for preventing the complications associated with this emerging infectious disease.
- In 1999, NIAID funded a fast-track project to develop a candidate West Nile virus vaccine with Acambis, Inc. Since then, scientists have developed a prototype vaccine and conducted initial feasibility studies. The vaccine is a chimeric vaccine (West Nile virus protein on a yellow fever vaccine). The Acambis vaccine has undergone preclinical evaluations in animals with encouraging results, and the company is moving forward with phase I trials.
- A DNA vaccine is being supported by NIAID.
- NIAID has funded investigators to establish a system to screen chemical compounds for possible antiviral activity against West Nile virus. Approximately 500 compounds have been screened, and several have moved forward to preclinical evaluation. NIAID also is supporting research on immunotherapeutics.
- NIAID supports the World Reference Center for Arboviruses, which has reference anti-West Nile sera and seed lots of various strains of West Nile virus. These reagents were provided when requested by investigators in the United States and Canada.
- NIAID supports research aimed at better understanding the vectors of transmission in affected areas. Such an understanding will allow improved monitoring and surveillance for the vectors and the viruses they transmit. NIAID also supports the development and preliminary testing of vector control strategies.

NIAID intramural scientists also have developed a West Nile virus vaccine candidate, which they have tested in mice with promising results. This vaccine candidate is a result of groundbreaking studies conducted nearly a decade ago in which scientists combined parts of different flaviviruses (a family of viruses including West Nile virus, dengue, Japanese encephalitis, and others) to make them weaker and thus more suitable for a live-virus vaccine. The West Nile virus vaccine uses part of the dengue virus as a backbone to which protective antibody-eliciting components of the West Nile virus are added.[35] Further testing of this vaccine candidate is ongoing, and development of other vaccine approaches, such as a full-length cDNA-derived West Nile virus vaccine, is under way. Following successful testing in nonhuman primates, investigators will prepare clinical lots of successful vaccine candidates for phase I to phase II testing in humans.

For more information on West Nile virus and NIAID's research portfolio in this area, please see *www.niaid.nih.gov/publications/wnile/default.htm.*

Tuberculosis

Mycobacterium tuberculosis (Mtb) kills more people globally than any other single infectious agent. It is estimated that one-third of the world's population (1.86 billion people) are infected with Mtb, and 16.2 million people currently have TB disease.[36-37] In 1999, an estimated 8.4 million persons developed TB, and 2 to 3 million patients died from this disease. Based on these statistics, TB kills more adults globally than any other single infectious agent.[38]

The majority of TB cases occur in developing nations. Although TB is essentially a treatable disease, lack of availability of drugs in many countries and poor adherence to treatment schedules due to side effects and the long duration of treatment (6 to 12 months) have resulted in the development of single and multi-drug-resistant strains of Mtb that result in TB that is much more difficult to cure. Furthermore, the link between HIV and TB is believed to be a major factor in the spread of TB. In 1997, of the 1.86 billion individuals worldwide who were infected with Mtb, approximately 10.7 million also were infected with HIV. In Africa, TB cases are increasing by 10 percent each year because of HIV. These factors, combined with a suboptimal public health infrastructure in many countries, contribute to the ongoing spread and re-emergence of TB worldwide.

NIAID served as secretariat and cosponsor of the Fourth World Congress on Tuberculosis, which was held June 3-5, 2002, in Washington, D.C. The meeting evaluated the state of the global TB epidemic since the last TB World Congress in 1992, with oral and poster presentations on topics in laboratory research, epidemiology, translational research, and health policy systems and services research. Approximately 800 participants from 58 countries attended the World Congress. The meeting cosponsors, donors, and organizers included the American Lung Association, American Thoracic Society, Bill and Melinda Gates Foundation, Coalition for TB Research and Development, Global Alliance for TB Drug Development, Infectious Diseases Society of America, International Union Against Tuberculosis and Lung Disease, Open Society Institute, Pittsfield Anti-TB Association, Rockefeller Foundation, Royal Netherlands TB Association (KNCV), Sequella Global TB Foundation, United Nations Development Programme/World Bank/WHO Special Programme for Research and Training in

Tropical Diseases, U.S. Agency for International Development, U.S. Centers for Disease Control and Prevention, U.S. Food and Drug Administration, U.S. NIH/NIAID and Fogarty International Center, Wellcome Trust, and WHO/Stop TB.

For additional information on NIAID TB research, see page 124.

Lyme Disease

Lyme disease (borreliosis) is the most prevalent tickborne infectious disease in the United States. Provisional cases of Lyme disease in the United States for the week ending October 26, 2002, numbered 13,734.

The major goals of the NIAID Lyme disease research program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities that are essential to increasing our understanding of the disease. The studies include both intramural and extramural research on animal models of disease, microbial physiology, molecular and cellular mechanisms of pathogenesis, mechanisms of protective immunity, vectors and disease transmission, efficacy of different modes of antibiotic therapy, and development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease.

NIAID intramural investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *Borrelia burgdorferi* in the early 1980s.[40] RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and relapsing fever microorganisms. Clinical investigators seek to better understand the natural history of chronic Lyme disease and possible causes for persisting symptoms. To this end, a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy is ongoing at the NIH Clinical Center. In addition, NIAID clinician/scientists assisted Tulane University colleagues in developing a new laboratory test for detection of acute and persistent Lyme infection. The assay, called C6 peptide ELISA, is accurate, simple to perform, and can be used to diagnose Lyme disease in patients who have received the Lyme disease vaccine. Lyme disease can be difficult to diagnose, especially in the later stages of infection when an individual's antibodies can fall to very low levels. Laboratory testing showed the C6 approach was highly sensitive for antibody detection during both the early and late stages of Lyme disease. The C6 ELISA test also resulted in fewer false positive readings when compared with earlier screening methods and will be of enormous value in assessing patients' response to therapy.[41] Another advantage is the test's ability to detect antibodies specific to both U.S. and European strains of *Borrelia*.

NIAID is also supporting an FY 2003 research initiative titled Partnerships for Novel Therapeutic, Diagnostic, and Vector Control Strategies in Infectious Diseases. This initiative will expand on an FY 2002 initiative of the same title. The goal of these initiatives is to support research and development of novel treatments for human infectious diseases of high public health impact or their arthropod vectors. One of the proposed research areas to be included in this initiative would be focused

on strategies for reducing vectorborne bacterial diseases, such as Lyme disease. A key component of this initiative is the development of partnerships among Government, academia, and the biotechnology and pharmaceutical industries.

Lyme borreliosis and ehrlichiosis will continue to be areas of high priority for basic research for the NIAID, especially with regard to (1) the characterization and treatment of acute and chronic infection, (2) the influence of coinfection with other vectorborne pathogens on the diagnosis, treatment, and severity of Lyme disease, and (3) the development of rapid, sensitive, and specific diagnostic tests and preventive strategies (e.g., vaccines and vector control measures).

Influenza

In the United States, pneumonia and influenza are the sixth leading cause of death, responsible for 3.7 percent of all deaths.[42] Research supported by NIAID has led to many new insights about how influenza causes disease.

The major goal of the NIAID influenza program is to support research leading to more effective approaches to control influenza virus infections. NIAID currently supports research in the following major areas:

- **Basic Biology**—Primarily through R01 grants, NIAID supports basic research on virus structure and function, viral pathogenesis, and the host response to infection.
- **Surveillance/Epidemiology**—NIAID supports research to better understand the natural history and emergence of influenza viruses with pandemic potential and to evaluate community-based strategies for interrupting the spread of influenza.
- **Vaccine Development and Evaluation**—Developing new influenza vaccines and strategies has been a major focus of the NIAID influenza program. These strategies include supporting the development of live-attenuated and recombinant vaccines, immunomodulators and adjuvants, cell culture-based vaccines, and basic research aimed at optimizing the immune response. NIAID also supports the production of pilot lot vaccines against avian influenza subtypes of high pandemic potential.
- **Public/Private Partnerships**—In 2000, NIAID awarded three challenge grants (required matching funds) to private-sector companies for the development of new vaccines against pandemic influenza strains. These companies are using live-attenuated viruses, virus-like particles, tissue culture substrates, and reverse genetics strategies to rapidly produce high-growth viruses for vaccine production. In 2003, NIAID's Partnership for Biodefense Initiative will be targeted at the private sector to support the development of anti-influenza drugs and novel influenza vaccines, including cell culture vaccines and strategies against pandemic influenza.
- **Drug Discovery and Evaluation**—NIAID supports the development of novel drugs against influenza and the evaluation of these new agents in both *in vitro* screening assays and in animal models.

NIAID has had a longstanding involvement in the development of a live-attenuated influenza vaccine and continues to support research in this area. For more than 25 years, NIAID has supported studies to evaluate the safety and immunogenicity of intranasally administered live-attenuated influenza vaccines, which have

been genetically altered to replicate only in the upper respiratory tract (temperature sensitive) and to cause only minimal symptoms (attenuated). Possible advantages of the live-attenuated influenza vaccine include the ability to induce a broader immune response and ease of administration.

The major focus of the NIAID influenza program will continue to be on basic and applied research that promises to further the development of new and improved vaccines and antiviral agents.

Prion Diseases

NIAID's Division of Intramural Research (DIR) has a productive and growing program focused on TSEs, or prion diseases. TSEs are fatal neurodegenerative diseases, such as scrapie, Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE or "mad cow" disease), and chronic wasting disease (CWD) of deer and elk. Since the BSE epidemic began in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In the fall of 2001, the emergence of BSE was reported in Asia when BSE-infected cattle were discovered in Japan.[43]

DIR TSE research is aimed at increasing our fundamental understanding of prion protein (PrP) and the mechanisms responsible for the accumulation of the abnormal form of prion protein (PrP-res) that appears to underlie TSE transmission and pathogenesis. Studies also are ongoing to elucidate the mechanisms of cross-species transmission of TSE disease, work that is highly important in light of the epidemiology of variant CJD as well as the prevalence of CWD in deer and elk herds in the western United States. DIR experiments have shown evidence that species that were once thought to be resistant to certain TSE strains can serve as lifelong carriers of the infection without ever becoming sick. Recent infrastructure improvements at NIAID's RML, including construction of new BSL-3 laboratory and animal facilities, have allowed expansion of TSE transmission studies. Preparations are nearly complete for an important study to determine whether CWD PrP can be transmitted to nonhuman primates via oral or intracerebral routes. These experiments will use CWD samples obtained through NIAID's collaboration with the Wyoming Department of Health.

DIR scientists also have discovered compounds that show promise as potential TSE therapeutics.[44] One class of compounds that will be tested for efficacy against TSE disease in rodents holds special promise as a drug therapy for TSEs because the compounds can be absorbed from the drinking water and concentrated in the brain.[45] Studies of the potential use of antibody and other vaccine-based therapies for TSEs are ongoing in NIAID laboratories. In addition, to advance earlier peptide studies, novel PrP peptides have been synthesized and are being evaluated for their ability to block the conversion of normal PrP to abnormal PrP-res *in vitro*. PrP peptides dispensed by direct injection or delivered by gene therapy might provide specific therapeutic treatment for TSE diseases. Promising compounds will be evaluated *in vivo* through a DMID contract with Utah State University. (See below.)

NIH provides grant support for investigator-initiated studies of CWD transmission. NIAID supports grants seeking to better understand

prion entry, trafficking, and neuroinvasion in the lymphoid system, which could provide a basis for development of diagnostic and intervention strategies. In addition, NIH has taken a number of actions in response to the 2001 BSE/TSE Action Plan, including the following:

- The establishment of a broad-based center for research on CWD at Colorado State University that will isolate, identify, and characterize strains of CWD; evaluate the potential for transmission (inter- and intraspecies) and pathogenesis of CWD; perform preclinical, animal-model-based evaluation of newly developed prophylaxes or therapies for CWD; develop, analyze, and distribute reagents, infectious material, molecular clones, and transgenic mice to the research community; and implement a systematic approach to furthering our understanding of the ecologic and environmental factors influencing the emergence, spread, and distribution of CWD and of the basic epidemiology and clinical aspects of these diseases.
- NIH is evaluating potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in transgenic animals that have a shortened time to death. This model was established at Utah State in collaboration with NIAID's RML.

Other Infectious Diseases and Deadly Pathogens

The Institute supports several unique international programs to promote scientific advances and cooperation on important infectious diseases and pathogens, both emerging and re-emerging, including the following:

- **International Collaboration in Infectious Disease Research (ICIDR).** The ICIDR program is designed to promote collaborative research between U.S. investigators and scientists in 15 countries where tropical infections are endemic. The ICIDR program was recompeted in 1999 with a companion program from the Fogarty International Center (FIC) titled Actions for Building Capacity (ABC), which supports the training of foreign investigators in the context of the ICIDR program. There are 14 NIAID-supported sites and four additional sites with support from the National Institute of Child Health and Human Development and the National Institute on Drug Abuse (NIDA). There are nine ABC awards in the ICIDR program.
- **ICIDR Opportunity Pool**. The pool was launched in fall 1999 to support research for emerging research opportunities due to unexpected disease outbreaks or scientific advances. To date, the ICIDR Opportunity Pool has supported research to evaluate the carriage of West Nile virus in birds migrating from the U.S. east coast to the Yucatan Peninsula, an investigation characterization of the Hantavirus outbreak in Panama, a project to evaluate genotypic and phenotypic correlation in *C. parvum* isolates from three different continents, and an investigation into the dengue outbreak in Bangladesh.

- **Tropical Disease Research Units (TDRUs)**. The TDRU program is a domestic grants award program intended to provide support for multiproject, interdisciplinary studies that seek to develop new strategies to control diseases caused by protozoa and helminths.

- **Tropical Medicine Research Centers (TMRCs)**. The TMRC program provides support to three foreign institutions (currently located in Peru, Brazil, and China) for research of direct relevance to the health of the people in tropical countries and to promote collaboration and exchange of information between foreign and American scientists. Three new TMRCs were awarded in 2002, including "New Tools to Understand and Control Endemic Parasites," to the Universidad Peruana Cayetano Heredia in Lima, Peru; "Pathogenesis of Leishmaniasis: Host, Parasite and Vector," to Federal University of Bahia in Salvador-Bahia, Brazil; and "Emerging Helminthiases in China," to the Chinese Academy of Preventive Medicine in Shanghai, China.

- **International Centers for Tropical Disease Research (ICTDR)**. The ICTDR network *(www.niaid.nih.gov/ictdr/default.htm)* consists of NIAID-supported centers focused on research in tropical diseases and includes approximately 22 international research sites in approximately 15 different countries. Investigators within ICTDR are supported by awards from the TDRU, TMRC, and ICIDR programs, as well as investigators from NIAID's intramural laboratories, especially the Laboratory of Parasitic Diseases. From April 15 to 17, 2002, NIAID sponsored the 11th Annual ICTDR Network meeting. This year's meeting included sessions on host genetics and tropical infectious diseases, influence of pathogen and vector genetics on transmission and disease manifestations, ecologic aspects of tropical diseases, tropical disease research in the context of the global HIV epidemic, and protective immunity and vaccine development.

- **U.S.-Japan Cooperative Medical Science Program**. A 36-year-old bilateral, cooperative research endeavor, this program involves U.S. and Japanese scientists who convene on a regular basis to address the public health priorities of Asia.

- **Vaccine Action Program (VAP)**. The Indo-U.S. VAP *(www.niaid.nih.gov/dmid/other/indo),* initiated in 1987, is a bilateral program that focuses on the development of safe and effective vaccines for major communicable diseases of interest to the two countries through joint research and development efforts. Currently, the focus of the program is on HIV/AIDS, malaria, and tuberculosis.

- **International Cooperative Biodiversity Groups Program (ICBG)**. NIAID continues to cosponsor the ICBG program, a project with a threefold mission—conservation of biodiversity, economic growth for developing countries, and discovery of pharmaceuticals from natural products. The National Cancer Institute, National Institute of Mental Health, National Heart, Lung, and Blood Institute, NIDA, FIC, National Science Foundation, and U.S. Department of Agriculture are the other cosponsors. Currently, there are six awards to multidisciplinary research groups that also include in-country, research-capacity strengthening activities, community

education programs, ethnobotanically based plant collections, and partnerships with a pharmaceutical company. ICBG investigators have achieved extensive progress in identifying bioactive compounds from plants of Central and South America, Nigeria, Cameroon, Madagascar, Laos, and Vietnam. The ICBG program has become widely recognized as a model for research partnerships that acknowledge intellectual property ownership of indigenous communities.

In FY 2002, NIAID extended its support and management of genome projects relevant to malaria (*www.niaid.nih.gov/cgi-shl/genome/genome.cfm*). The genome sequencing of *Plasmodium falciparum*, the most lethal malaria parasite, and of its mosquito vector, *Anopheles gambiae*, has been completed (*www.niaid.nih.gov/newsroom/releases/malariagenome.htm*). The publications of the genome sequences and related information appear in the journals *Nature* and *Science* respectively. The Malaria Research and Reference Reagent Resource Center (MR4) has provided support for the production of posters and CD-ROM informational material to accompany the publications of the *Plasmodium* and *Anopheles* genomes.

FINDING

Story of Discovery: Developing a Vaccine for West Nile Virus

The identification of West Nile virus (WNV) in New York in the summer of 1999 was the first time the mosquitoborne microbe had been detected in the Western Hemisphere. Until then, the virus had been found chiefly in Africa, Eastern Europe, the Middle East, and Asia. Since 1999, WNV has been reported in an ever-growing number of States within the United States. From 1999 to 2001, there were 149 confirmed cases of WNV in the United States, including 18 deaths. To date, in 2002, the number of confirmed cases and deaths in the United States already exceeds these numbers. Although infection with WNV usually causes only mild symptoms in humans, it can spread to the central nervous system and cause a potentially deadly brain inflammation called encephalitis, most common among the elderly. Currently, no treatment is available for WNV encephalitis, and no licensed vaccine exists to prevent the disease. Mosquito control has been the only available strategy to combat the rapid spread of this emerging disease, but effective spraying is difficult to carry out in urban areas.

Launching the Search for a Protective Vaccine

Faced with the potential for a serious WNV epidemic, NIH-supported researchers took swift action to develop a vaccine that protects against infection with the virus. Basic research on newly emerging microbes has enabled rapid progress in the development of a WNV vaccine. In addition, WNV vaccine development has benefited from the fact that WNV belongs to the group of viruses known as flaviviruses, which have many characteristics in common. These similarities have allowed scientists to build on earlier discoveries about other flaviviruses that are closely related to WNV, including Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), yellow fever virus (YFV), and dengue virus.

Developing Vaccines

There has been great success controlling yellow fever and Japanese encephalitis with well-organized vaccination campaigns centered on an efficacious vaccine. Therefore, NIH encouraged WNV vaccine development programs.

Importantly, NIH-supported basic research studies discovered that hamsters, and to a lesser extent mice, were good models for West Nile disease. NIH-supported researchers at the University of Texas Medical Branch, Galveston, conducted a series of preliminary experiments to learn more precisely the degree of protection that candidate WNV and other licensed flaviviruses vaccines might have against WNV. Researchers found that hamsters were completely protected by prototype WNV vaccines and, surprisingly, were at least partially protected by JEV and YFV vaccines.* Thus, this new model is an important new resource that could be used in the development of WNV vaccines to test the efficacy of a new vaccine candidate (or a new antiviral medicine).

NIH is supporting a number of vaccine approaches. One of the earliest started in 1999, when NIH funded a fast-track project to develop a candidate WNV vaccine with

⇨

Story of Discovery: Developing a Vaccine for West Nile Virus, Continued

Acambis, Inc. Since then, scientists have developed a prototype vaccine that has shown promise in animal tests. The vaccine is constructed using vaccine licensed for preventing yellow fever (caused by another flavivirus) as the backbone. For the WNV vaccine, researchers substituted the surface protein of WNV for the deleted YFV protein. This method of creating chimeric flavivirus vaccines also is being applied to developing a vaccine for dengue and JEV. The Acambis vaccine has undergone preclinical evaluations in hamsters, mice, monkeys, and horses with encouraging results. The company is moving forward with phase I trials. Vaccine is now being produced, and an investigational new drug (IND) application will be filed with the Food and Drug Administration. Trials are anticipated to begin in early 2003.

Other NIH scientists and collaborators from the Walter Reed Army Institute of Research (WRAIR) capitalized on recent advances in recombinant DNA technology and previous research on another flavivirus, called dengue virus, to produce a new candidate WNV vaccine. The NIH team already had successfully tested a strategy that used the new technology to replace key genes of different flaviviruses with those of dengue virus type 4 (DEN4). Unlike many flaviviruses, DEN4 does not cause disease in the brain. The resulting weakened, or attenuated, virus strains were safer for use in a vaccine but still protective.† The NIH-WRAIR research team then used this strategy to combine genes from WNV and DEN4. This hybrid virus did not infect the brain but still stimulated a strong immune response with even a single dose. When tested in mice, the hybrid vaccine protected all animals against lethal WNV infection. The findings from these studies provide the basis for pursuing the development of a WNV vaccine. The next step for the NIH-WRAIR research team is to test the promising hybrid vaccine in monkeys in late 2002. Progress to vaccine trials in humans is expected to be rapid because one of the dengue viruses used to construct the hybrid virus already has been proven safe in people.

Early studies also are under way on a DNA vaccine approach and a protein vaccine approach by other NIH-supported scientists.

Taking the Next Steps

By identifying successful strategies for vaccine development, NIH-supported studies are contributing to a major effort to slow the spread of WNV and avert a more serious public health threat from this emerging disease. ❖

*Tesh RB et al. Immunization with heterologous flaviviruses protective against fatal West Nile encephalitis. *Emer Infec Dis* 2002;8:245-251.

†Pletnev AG et al. West Nile virus/dengue type 4 virus chimeras that are reduced in neurovirulence and peripheral virulence without loss of immunogenicity or protective efficacy. *Proc Natl Acad Sci* 2002;99:3036-3041.

GENOMICS

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases supports a significant program in genomics research, including sequencing of human pathogens and invertebrate vectors of diseases, applying genomic technologies to the study of microorganisms and infectious diseases, supporting genomic databases, and providing access to high-quality genomic resources and technologies to the scientific community.

Genome Sequencing

Advances in molecular biology have led to remarkably fast and accurate methods for sequencing the genomes of disease-causing microorganisms and invertebrate vectors of diseases. Genome sequencing reveals the lineup of paired chemical bases that make up the pathogen's DNA, the language of life. When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes, and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Once virulence genes are found, researchers can attempt to disable them. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains, such as the spread of a virulent form of a pathogen in a susceptible population. Finally, understanding the genetic basis for both virulence and drug resistance also may help predict disease prognosis and influence the type and extent of patient care and treatment.

The potential payoffs of sequencing pathogens are enormous. NIAID scientists are exploiting sequence information in the following ways:

- To enhance the understanding of the disease-causing microorganisms and invertebrate vectors of diseases and their ability to cause disease;
- To facilitate the identification of novel and specific therapeutic targets for the development of new and improved drugs and vaccines, sequence-based detection technologies, and medical diagnostics for preventing, treating, and detecting infection;
- To compare the genomes of different species, strains, and clinical isolates to identify genetic variations and polymorphisms that may correlate with phenotypes, such as drug resistance, infectivity, morbidity, and virulence, and to identify targets for improving both forensic strain identification and molecular genotyping of microorganisms; and
- To trace microbial evolution.

Recognizing the tremendous benefits of genome sequencing, NIAID has funded a significant number of projects to sequence the full genomes of medically important microbes, including the bacteria that cause anthrax, plague, tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and foodborne diseases. In total, NIAID-supported investigators have completed genome-sequencing projects for more than 28 bacteria. NIAID's data release policies have ensured that the genome-sequencing data and their annotation are available on publicly accessible Web sites, before publication, for immediate access and use by the scientific community.

NIAID collaborates with other funding agencies to sequence the larger genomes of protozoan pathogens, such as the organism causing malaria, and invertebrate vectors of infectious diseases. The complete genome sequence of *Plasmodium falciparum*, the parasite that causes malaria, was published in 2002 and is based on the work of the International Malaria Genome Sequencing Consortium, which NIAID supports. In addition, NIAID supported the rapid sequencing of the genome of the malaria mosquito, *Anopheles gambiae*, which transmits the malaria parasite to humans. The genome-sequencing project has been completed and was published in 2002. The three genome sequences—the malaria mosquito, malaria parasite, and human—will provide scientists with a unique opportunity to study the natural history of malaria. For the first time, researchers will have the complete genetic information on an infectious organism, its natural host, and the insect that transmits the disease. NIAID-supported scientists have already taken advantage of this valuable genomic information and provided insights into the biology of the mosquito and parasite, molecular mechanisms involved in insecticide resistance, and gene and gene products that are potential targets for candidate drugs.

NIAID has made a significant investment in the genome sequencing of microorganisms considered agents of bioterrorism. NIAID is supporting sequencing efforts of several Category A, B, and C potential agents of bioterrorism. For example, the Institute supported the complete genome sequencing of *Bacillus anthracis* (Ames strain) in a collaborative effort with the Office of Naval Research and the Department of Energy. In collaboration with the Defense Advanced Research Projects Agency (DARPA), NIAID has funded the sequencing of *Brucella suis*, *Burkholderia mallei, Clostridium perfringens, Coxiella burnetii,* and *Rickettsia typhi*. In addition, NIAID has expanded its sequencing efforts of *B. anthracis* and has developed a comprehensive genomic analysis program that includes sequencing, comparative genomics approaches for more than 14 additional strains, clinical isolates, near neighbors, and related species. NIAID-supported scientists are using this genomic information for forensic strain identification and discovery of new targets for drugs, vaccines, and diagnostics for *B. anthracis*.

Genomic Research

NIAID-supported investigators are applying genomic and emerging technologies to study microorganisms and infectious diseases. This activity includes both basic research, such as studying the biology of the microorganism and host response to infection, and applied research, such as development of medical diagnostics, drugs, and vaccines. Genomic technologies are providing a new platform for scientists to study infectious agents at the whole genome or proteome level, providing clues to infectivity, pathogenesis, and virulence, as well as the host response to infection, vaccines, and drugs.

- Whole genome and proteome expression studies are being used to identify pathogen-specific genes involved in virulence, pathogenesis, and disease transmission.
- Proteomic technologies are being applied to characterizing the pathogen and/or host proteome, identifying protein targets for potential candidates for the next generation of vaccines, therapeutics, and diagnostics.
- Genomic technologies are providing platforms for examining genetic variation

in related species, strains, and clinical isolates and for studying host response to susceptibility to infection and effectiveness of vaccines and drugs.

Genome Resources, Reagents, and Technologies

NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, and to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate genomic and postgenomic data.

NIAID supports a Pathogen Functional Genomics Resource Center (PFGRC) *(www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm)* at the Institute of Genomic Research. The PFGRC was established in 2001 to provide and distribute to the broader research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. The scientific community has already had access to genomic resources such as DNA-based microarrays for functional genomic analysis of human pathogens.

NIAID supports the development of a haplotype genome map that will define haplotype blocks, which are the common ancestral chromosome segments observed in the major human populations. It is believed that a haplotype map is a necessary step toward effective genomewide scans for the association of genetic variation with disease risk and drug response in the human population. This genomic resource is being managed by the National Human Genome Research Institute and supported financially by many NIH Institutes.

NIAID participates in a trans-NIH initiative, the Mammalian Full Length cDNA Project, known as the Mammalian Gene Collection (MGC) (*http://mgc.nci.nih.gov)*. The goal of the MGC is to generate a full set of human and other mammalian full-length (open reading frames) cDNAs and to support the production of cDNA libraries, clones, databases, and repositories, which are accessible to the biomedical research community. Currently, the collection includes 12,414 human and 7,409 mouse full-length clones. These high-quality cDNA clones are a useful resource for the NIAID-supported scientific community for functional genomics and proteomics analysis of the host response to infection.

Bioinformatics and Databases

NIAID continues to provide support for databases of genomic and postgenomic information and analysis tools on sexually transmitted pathogens *(www.stdgen.lanl.gov)* and poxviruses *(www.poxvirus.org)*. DARPA transferred funds to assist NIAID in supporting this poxviruses bioinformatics resource center *(www.poxvirus.org)*, which includes a poxvirus genomic database, software for data analysis, a literature resource, and a repository of poxvirus species and strains, available at the American Type Culture Collection (ATCC). These databases are a valuable genomic resource, providing the scientific community with easy access to large amounts of genomic and related data and bioinformatics tools for data analysis.

Genomics and Proteomics

NIAID continues to collaborate with the National Institute of General Medical Sciences (NIGMS) on the NIGMS Protein Structure Initiative *(www.nigms.nih.gov/funding/psi.html)*, which supports research centers for the development of high-throughput methods

and structural determination of proteins. One project supports the determination and analysis of structures of more than 400 functionally relevant *Mycobacterium tuberculosis* proteins, and another project focuses on determining the protein structures from pathogenic protozoa. Structural and functional information on many proteins is now available in Web-based databases for access by the scientific community.

Division of Allergy, Immunology and Transplantation

The Division of Allergy, Immunology and Transplantation (DAIT) also supports genomics research. The human immune system is composed of complex networks of interacting cells, each programmed by precisely scripted genes. Underlying each immune response to a disease is a multistepped pathway of interacting molecules influenced by an individual's unique genomic characteristics. The immune system plays a critical role in diseases such as rheumatoid arthritis, hay fever, contact dermatitis, insulin-dependent or type 1 diabetes, systemic lupus erythematosus (SLE), and graft rejection of transplanted solid organs, tissues, and cells. Each of these diseases has an underlying genetic component.

Genomic research supported by DAIT is yielding insights into the functional and structural dimensions of immune system regulation, hypersensitivity and inflammation in diseases such as asthma, the dysregulation of immune responses that results in autoimmune disease, and basic mechanisms of immune tolerance and graft rejection. This research is important in the following areas:

- **Asthma and allergic diseases**. DAIT-supported research on the genetics of asthma, hypersensitivity, inflammation, and T-cell mediation enables us to understand the mechanisms underlying these immune responses, resulting in improved diagnostic, prevention, and treatment strategies. Through genomic research, DAIT-supported investigators discovered that interleukin-4 (IL-4), a cytokine that is produced by helper T cells and mast cells, stimulates antibody production by B cells in a series of reactions involving several genes. Further studies on IL-4 may provide a marker for measuring asthma risk and severity.

- **Autoimmune diseases**. DAIT supports research on type 1 diabetes and other autoimmune diseases that involve more than a single gene. Recent developments in genomics, such as high-resolution DNA analysis and bioinformatics tools, are making it possible to understand the underlying genetic causes of these complex diseases. For example, one approach compares the genes of individuals who have an autoimmune disease with those of healthy individuals to identify genetic and genomic differences that may be the underlying cause of disease. Between 10 and 20 distinct loci on the human genome may be responsible for susceptibility to type 1 diabetes. This knowledge will increase our ability to predict, diagnose, and treat this disease.

- **Transplantation**. DAIT-supported research on the genetics of graft rejection and immune tolerance is breaking new ground in the transplantation of solid organs, tissues, and cells for the prevention and treatment of disease. Genomic research funded by DAIT has identified surrogate markers of graft rejection in kidney transplant recipients. This research

holds promise for the development of a noninvasive predictor of graft rejection based on gene expression analysis in urinary cells of transplant recipients.

- **Basic immunology research.** Basic research in immunology furthers our understanding of the properties, interactions, and functions of the cells of the immune system and the genetic aspects of immune system regulation, and provides information about essential structural immunobiology. Recent breakthroughs in the basic science of immunogenetics inform clinical immunology, which may lead to the development of new immune-based therapies. Examples of basic immunology research supported by DAIT include the following:

  - Use of large-scale gene- and protein-expression-analysis tools to describe pathways of cellular activation;

  - Discovery of anti-inflammatory and immunosuppressive agents using DNA-based screening methods; and

  - Analysis of genomic databases of T-cell receptors and immunoglobulin gene sequences to link structural, functional, and clinical information.

Multicenter Research Programs

DAIT supports several multicenter research programs that include significant genomic efforts aimed at understanding the underlying mechanisms of immune-mediated diseases.

Immune Tolerance Network (ITN). The ITN is an international consortium of more than 70 basic scientists and clinical investigators established in FY 1999 to explore new approaches to selectively block or prevent the initiation of harmful immune responses. The potential impact of tolerance induction to improve human health is great, encompassing a broad range of immune-mediated disorders, including autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis; asthma and allergic diseases; and graft rejection in solid organ, tissue, and cell transplantation.

Genomic research now under way in the ITN may offer new therapeutic strategies for tolerance induction. The ITN is developing clinical trials of multiple tolerance-induction approaches for several autoimmune diseases, including multiple sclerosis and type 1 diabetes. The ITN also is pursuing clinical trials of multiple tolerance-induction approaches for asthma and allergic diseases, and currently supports a trial of DNA-ragweed-allergen conjugates for the treatment of allergic rhinitis. The network includes core laboratories to develop diagnostic assays to measure the induction, maintenance, and loss of tolerance in humans. These core facilities will develop and perform microarray analyses of gene expression, quantitative assays of T-cell reactivity, novel tissue morphology studies to analyze tissue changes due to disease progression and therapeutic efficacy, and bioinformatics approaches to analyze clinical and scientific data sets from the ITN-sponsored clinical trials.

Autoimmunity Centers of Excellence. These centers support collaborative basic and clinical research on autoimmune diseases, including single-site and multi-site pilot clinical trials of promising immunomodulatory therapies. The centers are presently enrolling participants in several clinical trials, including a trial of anti-CD20 in SLE and a trial of anti-C5 in lupus nephritis.

International Histocompatibility Working Group (IHWG). The IHWG is a network of more than 200 laboratories in more than 70 countries that applies new molecular techniques to population-based studies of histocompatibility genes. Histocompatibility genes allow the immune system to respond to specific pathogens, but these genes also play a role in the unwanted immune responses that occur in graft rejection and autoimmune diseases. Recent advances in genomics will facilitate the work of the human leukocyte antigen (HLA) class II genes and related polymorphisms and their role in immunity, disease susceptibility, and graft rejection. Genomic techniques developed by IHWG investigators and others have shown a greater diversity among histocompatibility genes than was previously detected by conventional serologic methods. This work will bridge the gap between serologic and genomic definitions of these genes.

Multiple Autoimmune Disease Genetics Consortium (MADGC). MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides materials to promote research aimed at discovering the human immune response genes involved in autoimmunity. MADGC began enrolling families in May 2000; to date, 121 families have been enrolled. More information can be found at *www.madgc.org*.

North American Rheumatoid Arthritis Consortium (NARAC). NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. More information can be found at *http://narac.patternrx.com*. This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation.

Primary Immunodeficiency Diseases Registry. This registry was established by NIAID through a contract with the Immune Deficiency Foundation to maintain clinical information on patients in the United States affected by primary immunodeficiency diseases. For each disease, the registry collects information on the natural course of the disease, including early and late complications, effects of therapy, and causes of death. The diseases included in the registry are chronic granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease (SCID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte-adhesion deficiency, and DiGeorge syndrome. Researchers may apply to the registry to obtain access to the patients for both basic research studies and clinical trials.

Federal Government/Industrial Collaboration. DAIT, in partnership with Roche Pharmaceuticals and Motorola, is supporting research projects that use bioinformatics to analyze clinical and gene-expression data that have been combined into one seamless database. This work, involving clinical data, rapid-throughput polymerase chain reaction, and gene chip and proteomics data, aims to determine the underlying immune

mechanisms responsible for the initiation and progression of end-stage renal disease (kidney failure) as well as acute and chronic kidney-graft rejection and long-term kidney-graft survival. This research models disease processes through a combination of sophisticated data-mining and hypothesis-based research to identify early markers of kidney-graft acceptance, rejection, and function. This Government-industry collaborative effort serves as a model for future programs in other immune-mediated diseases, particularly autoimmune disorders.

DAIT is collaborating with ProSanos Corporation, a clinical informatics software firm, and Management Science Associates, Incorporated, a world leader in large-scale database construction and management, to gain new insights into the immune mechanisms of kidney-graft rejection and survival. Newly developed software facilitates analyses across several clinical, epidemiologic, and genetic databases to perform sophisticated modeling of disease processes. The results of this project will lead to a greater understanding of the underlying immune mechanisms responsible for end-stage renal disease and acute and chronic kidney-graft rejection, yielding novel targets for therapeutic interventions to prolong graft survival.

In another DAIT-sponsored effort, Bioseek of Burlingame, California, is developing advanced flow cytometric-based methods to measure the expression of cell-surface molecules on endothelial cells—cells lining especially blood and lymphatic vessels. Such data will be useful in comparing the effects of various anti-inflammatory drugs and may provide the knowledge base necessary for the development of novel anti-inflammatory drugs.

The following is a list of NIAID-supported large-scale pathogen genome-sequencing projects in FY 2002:

Organism	Disease
Anopheles gambiae	malaria
Aedes aegypt	yellow fever
Aspergillus fumigatus	aspergillosis
Bacillus anthracis	anthrax
Bacillus cereus	gastroenteritis
Brucella suis	brucellosis
Brugia malayi	elephantiasis
Buckholderia mallei	glanders
Chlamydia pneumoniae	pneumonia
Chlamydia trachomatis	genital and chlamydia infections, trachoma
Clostridium perfringens	gas gangrene
Coccidioides immitis	respiratory infections; coccidioidomycosis
Coxiella burnetii	Q fever

NIAID-supported large-scale pathogen genome-sequencing projects in FY 2002, *Continued*

Cryptococcus neoformans	cryptococcosis
Cryptosporidium parvum	foodborne and waterborne diseases, gastritis
Ehrlichia spp.	ehrlichiosis
Entamoeba histolytica	dysentery
Enterococcus faecalis	nosocomial infections
Escherichia coli 0157:H7	gastritis, hemolytic, uremic syndrome
Escherichia coli K1	meningitis
Escherichia coli CFT073	urinary tract infections
Giardia lamblia	giardiasis
Haemophilus ducreyi	chancroid
Histoplasma capsulatum	histoplasmosis
Legionella pneumophila	Legionnaire's disease
Leishmania major	cutaneous leishmaniasis
Mycobacterium avium	pulmonary disease, opportunistic disease
Mycobacterium tuberculosis	tuberculosis
Neisseria gonorrhoeae	gonorrhea
Nematode species	helminthiases
Plasmodium falciparum	malaria
Pneumocystis carinii	pneumonia, opportunistic disease
Rickettsia rickettsii	Rocky Mountain spotted fever
Rickettsia typhi	typhus
Salmonella typhi	typhoid fever
Salmonella typhimurium	foodborne diseases, gastritis
Schistosoma mansoni	dermatitis, Katayama fever, liver inflammation, fibrosis
Shigella flexneri	shigellosis, hemolytic uremic syndrome
Staphylococcus aureus	surgical and wound infections, pneumonia, toxic shock syndrome
Staphylococcus epidermidis	bacteremia
Streptococcus pneumoniae	pneumonia, meningitis
Streptococcus pyogenes	strep throat, scarlet fever, pharyngitis, skin infections, necrotizing fasciitis, toxic shock syndrome, rheumatic fever
Toxoplasma gondii	toxoplasmosis, congenital, and ocular infections, opportunistic disease
Treponema pallidum	syphilis
Trichomonas vaginalis	vaginitis
Trypanosoma brucei	trypanosomiasis
Trypanosoma cruzi	Chagas' disease
Ureaplasma urealyticum	pelvic inflammatory disease
Vibrio cholerae	cholera
Wolbachia	endosymbiont of filarial nematodes and insect vectors
Yersinia pestis	plague

GLOBAL HEALTH

The NIAID research mission in infectious and allergic diseases is of global importance. When combined, these conditions are the most common causes of preventable human illness and death around the world. Recent concern about emerging and re-emerging infectious diseases and the anthrax biological weapon attacks of October 2001 further reinforced the importance of and added new dimensions to NIAID-supported research in improving early diagnosis, prevention, and control of these pathogens. Formal recognition of the importance of international research dates back to the International Health Act (1960), which gave the Secretary of Health and Human Services—formerly the Secretary of Health, Education, and Welfare—the authority to conduct research activities outside the United States, provided that the activities were beneficial to the health of U.S. citizens. This authority has been delegated to the NIH and to NIAID. The Public Health Service Act of 1988 (Public Law 100-607) created new HIV/AIDS authorities for the NIH. Subsequently, the NIH Revitalization Act (1993) gave NIAID specific authority to conduct research on tropical diseases that disproportionately affect populations in resource-poor and economically restructuring countries.

In May 2001, NIAID announced its *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. The Global Plan provides short-, medium-, and long-term objectives for treating, preventing, and controlling these diseases by building on the Institute's strong foundation in infectious disease research.

NIAID began developing a Biodefense Research Initiative in 2000. The President's FY 2003 budget proposed a massive expansion of this effort. During FY 2002, NIAID developed a strategic plan for biodefense and a research agenda for implementation. NIAID follows five basic strategies to carry out its international research activities.

Intramural Research Training and Collaborative Research

NIAID laboratories located in the Bethesda/Washington metropolitan area and Hamilton, Montana, are a significant source of research training for postdoctoral non-U.S. scientists. The host NIAID laboratory usually provides the stipend for the visiting scientist. The research training experience often results in long-term intramural international collaborations once the scientists return to their home countries. In FY 2002, the largest numbers of NIAID foreign scientists were from China, Italy, France, Japan, India, Russia, Australia, Germany, Canada, Korea, and Brazil.

NIAID laboratories become substantially involved in international research projects when these activities are essential to their research efforts. Funding ordinarily comes from the laboratory's regular budget and, for that reason, is not usually a major source of financial support. Exceptions may occur when the intramural laboratory is part of a consortium and/or the laboratory is able to secure extra-budgetary funding.

In collaboration with the NIH National Center on Minority Health and Health Disparities, the Fogarty International Center (FIC), and the University of Maryland, NIAID's Laboratory of Parasitic Diseases developed a training program for young U.S. scientists and medical students to gain experience in an African setting. Since 1989, the NIAID Laboratory of Parasitic Diseases has been working with scientists and physicians at the National School of Medicine

of Mali, located in Bamako, West Africa, to develop the Malaria Research and Training Center (MRTC). The Center has developed into a well-equipped, highly productive facility in which the research is planned, directed, and executed by Malian staff. Funding comes from a number of U.S. and international agencies, including several NIAID-funded U.S. universities. The MRTC recently dedicated a new laboratory research facility and dormitory.

Building on the experience in Mali, NIAID is developing the International Center for Excellence in Research (ICER) program, which has the objective of using longstanding intramural research to achieve long-term, sustainable collaboration and to attract extramural competitive funding. ICER projects are presently under development in India (tropical diseases), Papua New Guinea (malaria), and Uganda (HIV/AIDS).

Domestic Research Awards With a Foreign Component

NIAID funds the vast majority of its international research indirectly through competitive domestic extramural research awards that have a foreign component. Special emphasis programs have been developed in tropical medicine, emerging infectious diseases, HIV/AIDS, and tuberculosis to take advantage of research opportunities overseas in countries with a disproportionate burden of these diseases.

The NIAID International Centers for Tropical Disease Research (ICTDR) network is the earliest and most mature of these special programs. The ICTDR network consists of (1) Tropical Disease Research Units (TDRUs), which are U.S. institutions conducting multidisciplinary research relevant to the treatment, prevention, or control of tropical diseases, (2) the International Collaboration in Infectious Disease Research (ICIDR) program, which makes awards to U.S. institutions to engage in substantial international collaboration with overseas institutions in tropical medicine and emerging infectious diseases, (3) NIAID intramural laboratories active in tropical medicine and infectious disease research, (4) additional U.S. institutions with a critical mass of tropical and emerging infectious disease research, and (5) Tropical Medicine Research Centers, which provide direct funding to overseas centers of excellence. In FY 1999, NIAID formally linked the ICIDR program with the FIC Actions for Building Capacity (ABC) institutional research training program.

Initiated in 1994, the NIAID Tuberculosis Prevention Research Center has operated through a research contract with Case Western Reserve University to coordinate a consortium of U.S. and international (Brazil and Uganda) institutions to conduct a range of high-priority research projects that range from basic research to the development and evaluation of new or improved diagnostic tests, drugs, and vaccine candidates.

Each of NIAID's HIV/AIDS clinical research networks has international components. The HIV Vaccine Trials Network (HVTN) was created in May 2000 to advance worldwide efforts to develop an HIV vaccine. The network's U.S.-based units are integrated with sites around the globe to ensure appropriate vaccine approaches for these regions and to help the HVTN expand rapidly when it is ready to carry out large-scale studies of suitable vaccines. The HVTN international sites are located in Botswana, Brazil, China, the Dominican Republic, Haiti, Honduras, India, Malawi, Peru, South Africa, Thailand, and Trinidad and Tobago.

The HIV Prevention Trials Network (HPTN) is a second worldwide collaborative effort established by NIAID to evaluate the safety and efficacy of nonvaccine prevention interventions. To carefully evaluate the safety and efficacy of approaches such as topical microbicides and behavioral interventions, the HPTN consists of operational, data, and laboratory centers to support international research sites in Brazil, China, India, Peru, Russia, Thailand, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe. For a listing of the HVTN/HPTN U.S. and international locations, see page 15.

Foreign Awards

NIAID and the NIH accept investigator-initiated research proposals from foreign scientists and permit foreign scientists to respond to most program announcements (PAs) and requests for applications (RFAs). To be funded, foreign applications must receive a competitive peer-review score and be approved by the National Advisory Allergy and Infectious Diseases Council (NAAIDC) on the basis of their uniqueness and/or program relevance. Foreign scientists also may be eligible to compete for NIAID research contracts when U.S. institutions cannot carry out the project (e.g., pertussis vaccine trials in Italy and Sweden) or when the domestic applications are not responsive to the solicitation.

Historically, foreign awards have accounted for about 1 percent of the NIAID budget. As basic research results in new or improved products that require evaluation in populations with heavy burdens of disease, this amount is expected to increase. Furthermore, long-term NIAID investment in collaborative research has resulted in the development of overseas sites capable of independent research. The establishment of the Tropical Medicine Research Center (TMRC) program a decade ago was a reflection of this phenomenon.

In FY 2001, NIAID launched the Comprehensive International Program for Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. As national research capacity grows, countries can seek renewable CIPRA funding for multidisciplinary research projects and/or clinical trials for HIV prevention and/or treatment.

CIPRA now funds three such multidisciplinary research projects in China and South Africa. Planning and organizational grants have been awarded to Brazil, Cambodia, the Congo (Brazzaville), the Dominican Republic, India, Mexico, Peru, Russia, Tanzania, Thailand, Trinidad and Tobago, Vietnam, and Zambia.

Official Bilateral Programs

In addition to regular scientific channels, the United States often develops formal, bilateral scientific agreements with foreign governments or organizations at the Presidential, Department of Health and Human Services, NIH, or NIAID level. NIAID carries out these programs with budgeted funds unless special or supplementary funds are made available. During FY 2001, NIAID actively participated in bilateral programs involving Brazil, China, France, the Republic of Georgia, Germany, India, Italy, Japan, Russia, South Africa, and Taiwan. Of particular interest is the U.S.-Japan Cooperative Medical Science Program (USJCMSP), which consists of committees of senior scientists and panels of experts in high-priority diseases of

the Pacific Basin. Both the Joint USJCMSP Committee and Joint Panels meet annually, alternating countries in conjunction with scientific conferences. The USJCMSP also has organized annual workshops on emerging and re-emerging infectious diseases in the Pacific Basin at different sites in the region. Active priority areas are AIDS, acute respiratory infections, cholera and other bacterial enteric diseases, environmental mutagenesis and carcinogenesis, infectious hepatitis, immunology, leprosy/tuberculosis, nutrition, parasitic diseases, and viral diseases.

International Agencies and Organizations

NIAID has joined with other organizations to enhance scientific collaborations in combating infectious diseases. Examples include the Presidential Millennium Vaccine Initiative; the Global Alliance for Vaccines and Immunization (GAVI); the Multilateral Initiative on Malaria in Africa (MIM); the International Cooperative Biodiversity Groups Program; and the DHHS-State Department BioTechnology Engagement Program (BTEP) and the Civilian Research and Development Foundation (CRDF), both of which provide support to scientists in the Newly Independent States to conduct collaborative research on problems of public health importance.

NIAID staff members also participate on the scientific boards of and as consultants to the World Health Organization, the Pan American Health Organization, and the U.S. Agency for International Development.

HEPATITIS C

Hepatitis C is an emerging disease in the United States and worldwide. Before 1990, transfused patients were vulnerable to an unidentifiable liver disease agent(s) known only as non-A, non-B hepatitis. Cloned and sequenced more than a decade ago, hepatitis C virus (HCV) was identified as the cause of most of these chronic infections. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV remains the leading reason for liver transplants in this country. Rapid improvements in HCV diagnostics have occurred both in terms of antibody detection and the presence of the virus directly, making the supply of blood and blood products in the United States very safe. New infections continue at the rate of 25,000 cases a year in the United States *(www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm)*.

Today, injection drug users are at highest risk, yet transmission also occurs sexually (greatest with multiple partners) as well as through other mechanisms involving inadvertent exposure to contaminated blood. Estimates today indicate that HCV is carried by more than 170 million people worldwide,[46] with 4 million in the United States alone *(www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm)*. Approximately 75 percent of those infected become chronic carriers, many of them unknowingly. They manifest no overt signs of liver morbidity for decades while their livers are undergoing active disease progression *(www.cdc.gov/ncidod/diseases/hepatitis/c/faq.htm#1g)*.

NIAID has aggressively pursued the expansion of HCV research through its development of the Hepatitis C Framework for Progress. With the aid of participating Institutes and Centers, an NIH-wide framework was drafted that incorporates the different missions into a cohesive global plan. The final plan was reviewed by outside experts and has been approved by both the NIH Institute and Center Directors and the NIH Director. The following research goals were identified in the framework:

- Understanding transmission modes to develop effective intervention strategies;
- Understanding pathogenic mechanisms and disease progression to develop treatments;
- Characterizing hosts' immune responses to infection to develop vaccines and prophylactic measures as well as therapeutic measures;
- Defining viral replication and recovery with therapy as well as developing new therapeutic strategies;
- Investigating clinical manifestations to develop noninvasive methods to evaluate current disease state, to predict outcomes, and to prevent or reverse disease progression; and
- Defining effective prevention and intervention strategies to improve health.

The tools needed to develop these goals include tissue culture systems, small-animal models, and well-defined clinical cohorts.

Current therapies include various forms of interferon, an interferon-ribavirin combination, and long-lasting forms of interferon with and without ribavirin. Each iteration has improved response rate. Unfortunately, these drugs have a significantly lower success rate in patients infected with the viral genotype that predominates in the United States, as well as in

African Americans. Genotype refers to the genetic makeup of an organism or a virus. At least six distinct HCV genotypes have been identified, and genotype 1 is the most common genotype found in the United States. Studies suggest that African Americans with genotype 1 treated with interferon for HCV have a lower end-of-treatment response than Caucasians.[47] Therapeutic targets are being addressed, including inhibitors of viral components, such as the polymerase, protease, helicase, and internal ribosome entry site, and other viral enzymes critical for replication.

Vaccine development for HCV will require increased understanding of the protective immune response and of viral immune evasion tactics. These areas can best be studied in individuals with acute (early) infection.

In 2002, NIAID cosponsored the Management of Hepatitis C, 2002, Consensus Development Conference. The meeting was convened to provide an update to a 1997 conference on the same topic. Among its recommendations for future research, the panel gave top priority to the development of reliable and reproducible HCV cultures, which will advance the understanding of its biology and mechanisms of drug resistance and aid vaccine development. The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C. NIAID supports a robust hepatitis C research portfolio that encompasses many of these areas. In particular, NIAID supports the Hepatitis C Cooperative Research Centers Network, which unites basic and clinical researchers investigating hepatitis C infection and the disease process to identify new and better means of prevention and treatment. Through this network, NIAID supports a clinical trial examining pegylated interferon plus ribavirin in parallel cohorts of African Americans and Caucasians in an effort to sort out the causes of disparities between these two groups in standard treatment. NIAID also continues to provide partial support for the ancillary studies of the HALT-C trial of the National Institute of Diabetes and Digestive and Kidney Diseases. The trial is evaluating the impact of long-term therapy on disease progression, including virologic and immunologic responses and their association with recovery.

Scientists at NIAID's Division of Intramural Research (DIR) are conducting research on the mechanism that leads to the transition from asymptomatic infection to chronic infection and recovery in response to therapy. This work includes studies of the relative importance of the virus versus the host immune response in determining the outcome of infection. Scientists are using standardized amounts of a single genetic strain of HCV to study the natural history of chronic hepatitis C in chimpanzees by mapping the mutations that occur over time. Additional studies will focus on the types of genetic mutations that help HCV evade the immune system and on the types of antibodies produced during the early immune response. In addition, various approaches to answering key questions about HCV pathogenesis and the host immune response are being pursued by extramural scientists. Understanding these phenomena will allow the development of new tools for hepatitis C treatment and prevention.

In addition, NIAID intramural investigators are accelerating research to develop an HCV vaccine. To this end, they have prepared and standardized doses of HCV that can be used to test the effectiveness of candidate vaccines in the chimpanzee and have distributed this key reagent to the scientific community. Intramural

scientists also have developed and tested candidate DNA vaccines for HCV in chimpanzees. They also are evaluating vectored vaccines. Although these experimental vaccines did not prevent infection, they did modify the course of the infection. Several NIAID grantees also are working to develop an HCV vaccine.

Vaccine studies are hampered by the lack of a small-animal model or an *in vitro* system in which to study HCV and fine-tune possible vaccine formulations. To address both the lack of a small-animal model and the poor growth of wild-type HCV *in vitro* (cell culture), DIR researchers are genetically manipulating HCV to identify an infectious cDNA of HCV that can replicate *in vitro* and *in vivo*. Preliminary results of this work showed that mutations allowing replication of the HCV genome in cell culture markedly weakened the virus for replication *in vivo*. This finding suggests that extrapolation of results obtained in the *in vitro* system to the clinical setting must be done with caution.

IMMUNE TOLERANCE

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and rejection of transplanted solid organs, tissues, and cells.

Tolerance induction approaches seek to selectively block or prevent deleterious immune responses. For example, in transplantation, donor-specific immune tolerance—a selective blockade of immune responses directed against the graft—would enable long-term graft survival without the complications and risks of systemic immunosuppressive therapy (e.g., infection, malignancy, and atherosclerosis). In asthma and allergic diseases, the goal of tolerance research is to develop methods to block immune responses, especially allergic (IgE) responses, to allergens, such as cockroach and house dust mite, that cause or exacerbate these diseases. In autoimmune diseases, tolerance-induction approaches seek to block those immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Two decades of highly intensive and productive basic research in immunology have provided a solid foundation of knowledge and understanding that will enable the application of promising tolerance-induction strategies to the treatment of human disease.

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports basic research to elucidate mechanisms responsible for immune tolerance, translational research to facilitate the application of immune tolerance approaches to human diseases, and clinical research to evaluate novel therapeutic approaches to induce and maintain immune tolerance in humans. New approaches are being sought to accomplish the following:

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve currently suboptimal treatment protocols for immune-mediated diseases;
- Discover methods to prevent or reverse immune-mediated disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

In FY 1999, DAIT established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases and to preventing the rejection of transplanted kidneys and pancreatic islets. The goal of these therapies is to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. An important aim of the ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate drugs. The ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. Since its inception, the ITN has initiated more than 21 clinical protocols; established approximately 5 studies to explore immune mechanisms leading to the development, maintenance, or

loss of clinical tolerance; and established a variety of state-of-the-art core facilities.

As clinical therapies for inducing tolerance are advanced, it becomes essential to develop procedures to monitor patient progress and provide physicians with tools for assessing the ongoing ability to maintain a tolerogenic state. These mechanistic assays are termed "tolerance assays." The ITN has established a set of core laboratories to develop diagnostic assays for the induction, maintenance, and loss of tolerance. These core facilities include microarray analyses of gene expression, bioinformatics approaches to develop analytic tools for clinical and scientific data sets from the ITN-sponsored trials, ELISPOT analyses of protein expression, and cellular assays for T-cell reactivity.

ITN studies include the following:

- The "Edmonton Protocol," an experimental islet transplantation protocol for patients with hard-to-control type 1 diabetes.
- A phase II multicenter trial to evaluate the potential for treating patients with new-onset type 1 diabetes with anti-CD3 antibody to prevent the loss of insulin-producing cells. This study will further assess the safety and efficacy of anti-CD3 antibody and the capacity of this regimen to promote the induction of long-term immunologic tolerance to the autoantigens associated with type 1 diabetes.
- A trial to evaluate combined bone marrow and kidney transplantation for patients with kidney failure caused by complications of multiple myeloma. The Massachusetts General Hospital has successfully treated two patients using this regimen, including complete withdrawal of all antirejection drugs. The ITN is supporting a multicenter trial of this protocol to further assess its efficacy and is conducting important scientific studies to understand the mechanisms of tolerance induction using this regimen. As with all ITN-supported clinical trials, this study will integrate research to identify the underlying immune mechanisms involved in disease progression and therapeutic effect.
- Studies to analyze the immune responses of liver and kidney transplant recipients who have maintained their transplanted organs for many years, despite discontinuation of antirejection therapy. Investigators will explore the immune mechanisms responsible for long-term antirejection and drug-free graft survival and will determine whether these patients have developed immune tolerance to their transplanted organs.
- Clinical trials involving multiple tolerance-induction approaches for several autoimmune diseases, including multiple sclerosis and type 1 diabetes. The ITN also is pursuing clinical trials involving multiple tolerance-induction approaches for asthma and allergic diseases and currently supports a trial of DNA-ragweed allergen conjugates for the treatment of allergic rhinitis.

More information on the ITN is available on its Web site at *www.immunetolerance.org*.

In FY 2001, NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases issued a Request for Applications to renew and expand the Non-Human Primate Transplantation Immune Tolerance Cooperative Study Group. This group was established in FY 1999 to evaluate the safety and efficacy of tolerogenic regimens in large-animal models of

kidney and pancreatic islet transplantation. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplant recipients.

Other DAIT-supported research programs that include studies on immune tolerance are the Autoimmunity Centers of Excellence, the Human Immunology Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance.

MALARIA

Malaria, a serious disease caused by a parasite transmitted by a mosquito, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Because of variations in the parasite species that cause malaria, the development of a successful vaccine has been difficult. Globally, malaria causes more than 1 million deaths each year, primarily in children. According to the World Health Organization (WHO), malaria accounted for an estimated 1.08 million deaths and more than 40 million lost disability-adjusted life years in 2000.[48] The situation is worsening because efforts to control malaria are severely hindered by the spread of drug-resistant parasites and insecticide-resistant mosquitoes.

Malaria research at the NIH dates back to the 1930s, a time when malaria was a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID activities in malaria include a broad portfolio of research on parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector control, conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories, and overseas.

NIAID has a large intramural program, the Malaria Vaccine Development Unit (MVDU), dedicated to malaria vaccine development. The MVDU is collaborating with a number of investigators within the United States and throughout the world to contribute to this effort, as well as with the extramural NIH malaria program and with a variety of funding agencies, such as the U.S. Agency for International Development (USAID) and the Gates Malaria Vaccine Initiative. The MVDU has produced six potential vaccine products using the quality control practices required for manufacturing clinical materials. An investigational new drug (IND) application for one vaccine formulation, called Pvs25, has been submitted to the U.S. Food and Drug Administration, and two more IND applications are in preparation. Following IND approval, phase I clinical studies will be conducted in the NIH Clinical Center. When vaccine formulations are found to be safe and capable of eliciting an immune response, further phase I and phase II testing will be conducted in collaboration with colleagues at the NIAID-supported Malaria Research and Training Center in Mali, West Africa, or at other suitable field sites.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, using genetic methods, NIAID scientists have traced the *Plasmodium falciparum* strains in the world today to an ancient ancestor that existed 100,000 to 180,000 years ago and showed that the parasite is genetically more diverse than some scientists had thought.[49] Generally, greater parasite genetic diversity makes developing an effective vaccine formulation more difficult. In addition, NIAID scientists are characterizing molecules that determine the *P. falciparum* parasites' response to chloroquine and quinine, with a view toward new therapeutic strategies and diagnostics for the detection of drug-resistant malaria. To understand the factors that determine the severity of malaria, NIAID investigators are studying how hemoglobin C and hemoglobin S (sickle-cell hemoglobin) protect children from severe and fatal complications of *P. falciparum* malaria.

Antigens are substances that provoke immune responses. NIAID studies of the mechanisms by which parasites coordinate the silencing and activation of certain genes that are responsible for antigenic variation in malaria are clarifying how parasitized red blood cells avoid destruction by the human immune system. To further their discovery of a novel feeding channel through which malaria parasites uptake nutrients while infecting red blood cells, NIAID scientists are evaluating these channels as potential new targets for future antimalarial vaccines or chemotherapies.[50]

To complement laboratory-based research, NIAID-supported investigators are conducting clinical and field-based studies of malaria in endemic regions, including Brazil, Cameroon, Ghana, Indonesia, Malawi, Mali, Papua New Guinea, and Thailand.

In 1997, the Institute developed a multiyear plan to accelerate research on malaria vaccine development. The plan emphasizes the following:

- Improved access to well-characterized research materials,
- Discovery and preclinical testing of new vaccine candidates,
- Production and evaluation of candidate vaccines, and
- Clinical research and preparation for clinical trials in endemic areas.

As early steps in implementing this plan, NIAID established a repository of well-characterized malaria research reagents, contributed to the sequencing and analysis of the genomes of *P. falciparum* and *Anopheles gambiae*, and expanded current malaria vaccine production and evaluation efforts through collaborations between intramural and extramural scientists. Some noteworthy aspects of NIAID-supported research carried out in FY 2002 include the following:

- In FY 2002, NIAID extended its support and management of genome projects relevant to malaria *(www.niaid.nih.gov/cgi-shl/genome/genome.cfm)*. The genome sequencing of *P. falciparum*, the most lethal malaria parasite, and of its mosquito vector, *A. gambiae*, has been completed *(www.niaid.nih.gov/newsroom/releases/malariagenome.htm)*. This information, together with the human genome information, will enable scientists to better understand the disease and its transmission and should pave the way for new drugs, vaccines, and insecticides that will more effectively control malaria.
- NIAID also continued to pursue the systematic implementation of its Malaria Vaccine Research Plan, designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety evaluation of promising candidate vaccines before entry into clinical trials. Reagents also were provided to the Malaria Research and Reference Reagent Resource (MR4), a NIAID-supported central source of quality-controlled malaria-related

reagents and information, which will make them available to the international malaria research community.

- NIAID issued an RFA titled "Partnerships for Novel Therapeutic, Diagnostic, and Vector Control Strategies in Infectious Disease," which solicited applications for projects that included substantive involvement from the private sector; awards will be made at the end of FY 2002. The rationale underlying this initiative was that product development expertise is found in private companies and that the financial investment from NIAID would stimulate them to contribute to disease areas that are perceived as providing limited return on investment. In response to this RFA, applications were reviewed and two malaria-related applications were funded. One of these projects seeks to develop new drugs for malaria using a combination of state-of-the-art functional genomics technologies and combinatorial chemistry. The other project seeks to develop new environmentally safe insecticides targeting mosquito activities.

- NIAID continues to collaborate and coordinate with other Federal agencies, such as USAID, the Centers for Disease Control and Prevention, and the Department of Defense, to accelerate the research and development of malaria vaccines. NIAID also is a founding member of the Multilateral Initiative on Malaria (MIM), a consortium of research-funding agencies created to improve global collaborations in malaria research. MIM works closely with WHO's Roll Back Malaria Program and others to ensure that research findings are applied to improve malaria control.

MINORITY AND WOMEN'S HEALTH

The Office of Special Populations and Research Training (OSPRT) provides oversight and coordination to the Institute's activities in the area of minority and women's health. In FY 2002, OSPRT updated the NIAID *Strategic Plan on Health Disparities* to indicate progress made in meeting the goals established in FY 2000-2001. The plan focuses on three goals: (1) to conduct research to identify and address health disparities among various populations affected by infectious and immunologic diseases, (2) to increase the number of minority scientists and grantees, and (3) to improve education and outreach activities for the transfer of health information to these populations. As outlined in the *Strategic Plan for Addressing Health Disparities*, NIAID continues to prioritize basic, clinical, and epidemiologic research on these health problems; efforts to increase participation of minority scientists in its research; and outreach activities designed to communicate research developments to these populations. The plan is available online at the following NIAID Web site as an Adobe document: *www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf*.

For more than 50 years, NIAID has contributed to the progress made in understanding, treating, and preventing infectious and immunologic diseases known to occur disparately in minorities and women. NIAID's research agenda addresses several autoimmune and infectious diseases that disproportionately affect both populations. NIAID maintains a rigorous effort to ensure that all racial and ethnic backgrounds participate in its clinical trials. In many clinical trials, the rate of participation exceeds the rate of incidence for several minority populations, especially in the area of AIDS research. Differences in racial and ethnic backgrounds can affect susceptibility to infectious and immunologic diseases, including AIDS, asthma, sexually transmitted diseases (STDs), and kidney disease. Moreover, minority populations often do not fully reap the benefits of research advances that have helped improve the health of other Americans.

Minority Health

Asthma morbidity and mortality have been increasing in the United States for the past 15 years and are particularly high among poor, African-American, inner-city residents. NIAID's National Cooperative Inner-City Asthma Study (NCICAS, 1991-1996) developed a successful educational, behavioral, and environmental intervention. The current study (1996-2002), cofunded by NIAID and the National Institute of Environmental Health Sciences (NIEHS), is a multicenter trial that is testing the effectiveness of two interventions in reducing asthma morbidity and severity among inner-city children ages 5 to 11 with moderate to severe asthma. NIAID is collaborating with the Centers for Disease Control and Prevention (CDC) to launch a program to disseminate and implement the NCICAS intervention.

In FY 2003, NIAID plans to fund an Inner-City Asthma Consortium and Statistical and Clinical Coordinating Center to support a network of scientists who will evaluate the safety and efficacy of promising immune-based therapies aimed at reducing asthma severity and preventing disease in inner-city children. This study is in addition to its eight Asthma and Allergic Diseases Research Centers (AADRCs), which provide support for basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases.

Some autoimmune diseases disproportionately affect minorities, especially minority women. For example, systemic lupus erythematosus (SLE) and scleroderma disproportionately afflict African-American women. Organ transplantation represents a health disparity for African Americans and Asian Americans, who receive fewer transplants than would be expected from their representation on the transplant waiting list. NIAID supports basic, preclinical, and clinical research on transplantation immunology, and demonstration and education research projects to increase organ donation among minority populations.

NIAID is addressing these conditions and disparities in a number of research projects. NIAID, with several other NIH components, established the Centers for Prevention of Autoimmune Diseases to support basic research that will build the knowledge base needed to develop new targets and approaches to preventing autoimmune disease. NIAID is also expediting awards to support clinical studies associated with immunotherapies for autoimmune diseases and other immune-mediated diseases. The Institute also is planning to support multidisciplinary research targeting the identification, characterization, and definition of gender-based differences in the immune response.

The Immune Tolerance Network (ITN), established by NIAID in 1999, is an international consortium of approximately 80 scientists and clinical investigators who are testing promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. ITN is developing multiple tolerance induction approaches for multiple autoimmune diseases.

Hepatitis C virus (HCV) infection is the most common chronic bloodborne viral infection in the United States. Various surveys indicate that HCV disproportionately affects minority populations; moreover, available treatments for HCV tend to be less effective for African Americans than other populations.[51] NIAID currently funds 45 HCV grants and 6 Hepatitis C Cooperative Research Centers (HC CRCs). The HC CRCs make up a research consortium whose goals are to identify components of HCV and the body's immune response, as well as individual genetic factors that have a crucial impact on recovery from initial and chronic infection, disease progression and severity, and the influence of cofactors that affect HCV disease.

During 2000, approximately 78 percent of active tuberculosis (TB) cases were reported among racial and ethnic minorities.[52] The problems of urban poverty, high HIV infection rates, and the effects of household crowding may contribute to the disproportionate impact of TB on minorities. Over the past decade, dramatic increases in NIAID funding for TB research have allowed the Institute to support a wide range of TB initiatives and an expanded community of TB researchers. NIAID's extramural TB research program supports more than 150 grants for basic and applied TB research, including awards to support the genomic sequencing of *Mycobacterium tuberculosis*, the bacterium that causes TB, as well as other related mycobacterial species. NIAID also continues to support the Tuberculosis Research Unit at Case Western Reserve University, which conducts multidisciplinary laboratory and clinical studies to answer critical questions in human TB; provides knowledge, tools, and technologies to improve clinical trials in TB; and offers the ability to conduct clinical studies for the

evaluation of new or improved vaccines, therapeutics, and diagnostics *(www.tbresearchunit.org)*.

One of NIAID's high-priority goals is the development of improved TB vaccines, as outlined in the Institute's *Blueprint for Tuberculosis Vaccine Development*. Through the TB research materials and vaccine-testing contract, NIAID provides TB research reagents and offers testing services for vaccine candidates in animals to qualified investigators throughout the world.

Sexually transmitted diseases (STDs) are critical global and national health priorities because of their devastating impact on women and infants and their causal association with HIV infection. Reported rates of some STDs, such as gonorrhea and syphilis, are as much as 30 times higher for African Americans than for whites. This disparity is due to many factors, including differences in the distribution of poverty, health-seeking behaviors, and access to quality health care.[53]

NIAID supports research for more effective prevention and treatment approaches to control STDs. The Institute's ongoing efforts include the STD Cooperative Research Centers, the STD Clinical Trials Unit, and the Topical Microbicides Program projects. In addition, NIAID continues to initiate and support a variety of other research projects that focus on (1) developing vaccines, topical microbicides, and treatments for the microbes that cause STDs; (2) developing better and more rapid diagnostics; (3) sequencing the genomes of sexually transmitted pathogens; and (4) understanding the long-term health impact of sexually transmitted pathogens in various populations.

AIDS continues to affect minorities disproportionately. In absolute numbers, African Americans have outnumbered whites in new AIDS diagnoses and deaths since 1998. Of the new AIDS cases reported in 2001, 49 percent were among African Americans, 20 percent among Hispanics, 30 percent among whites, and less than 1 percent among American Indians/Alaska Natives and Asian Americans/Pacific Islanders. Among women, African Americans and Hispanics account for 80 percent of AIDS cases; among men, African Americans and Hispanics account for 63.3 percent of cases.[54]

One of the greatest challenges facing AIDS researchers today is the recruitment and retention of minorities for clinical trials. As the epidemic expands into minority communities, inclusion of these individuals in clinical trials is particularly urgent to ensure that the results of research are applicable to all populations affected by the disease. An additional challenge is the recruitment of underrepresented minority investigators to AIDS and AIDS-related clinical and basic research disciplines. To address this, NIAID supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing and treating HIV disease in minority communities, training minority investigators, and fostering infrastructure development.

Each of NIAID's large, national therapeutic clinical trials networks, namely, the Adult AIDS Clinical Trials Group (AACTG), the Terry Beirn Community Programs for Clinical Research on AIDS, and the Pediatric AIDS Clinical Trials Group (PACTG), strives to ensure enrollment of a sufficient proportion of minority subjects.

NIAID's epidemiologic research explores the clinical course and factors contributing to transmission of HIV infection in a variety of populations. Groups of inner-city women and their children are the focus of the Women and Infants Transmission Study (WITS), and the Women's Interagency HIV Study (WIHS) includes both HIV-infected and uninfected women. Both WITS and the Multicenter AIDS Cohort Study, a prospective longitudinal study of HIV disease in homosexual and bisexual men, are studying access to medical care among people of minority backgrounds.

The HIV Vaccine Trials Network (HVTN) is dedicated to developing an HIV vaccine through testing and evaluating candidate vaccines in clinical trials. The HVTN also has initiated community outreach programs to educate people about HIV and vaccine research and to encourage participation in clinical trials. Through these outreach activities, the HVTN hopes to enroll a diversified population in its clinical trials, with an emphasis on recruiting minorities and women. NIAID also has established the National HIV Vaccine Communications Steering Group, which is charged with developing and implementing a national information campaign to promote HIV vaccine awareness and education in both affected communities and the general public. Educating the community about HIV clinical trials is also an important part of outreach for the HIV Prevention Trials Network (HPTN), which is exploring nonvaccine prevention strategies to reduce HIV transmission at U.S. and international sites.

NIAID research to prevent mother-to-child transmission of HIV is conducted through both the HPTN and the Pediatrics AIDS Clinical Trials Group. Research in this area includes ongoing trials that are evaluating simpler and less costly prevention regimens suitable for global use. NIAID also supports the Centers for AIDS Research, which address problems in the enrollment and retention of women and minority groups in AIDS clinical trials and promote the development of minority scientists in AIDS research.

Minority Researchers' Training and Enhancement Programs

Increasing the participation of underrepresented minority investigators in virtually all fields of biomedical research is a continuing NIH and NIAID priority. In addition to supporting NIH-wide programs, NIAID has developed and supported a variety of innovative minority programs for biomedical research, encompassing high school through postdoctoral training.

OSPRT continues to administer the extramural Introduction to Biomedical Research Program and the Bridging the Career Gap for Underrepresented Minorities Workshop. These two programs target students from the high school level to the postdoctoral level.

In October 2001, NIAID held its fifth symposium on Bridging the Career Gap for Underrepresented Minority Scientists. This initiative nurtures the research careers of individuals currently funded under various NIAID minority training and enhancement programs. The next Bridge symposium will be held in October 2003.

NIAID also collaborates with minority organizations to disseminate information about biomedical research careers to members of underrepresented groups. The Institute provides funding to the Interamerican College of Physicians and Scientists' Hispanic Youth Summer Program, which seeks to introduce Hispanic youth to careers in biomedical

research through scientific seminars and field trips. NIAID also supports summer programs at the NIH for Hispanic and Native American students.

NIAID continues to work with schools on several programs that foster an interest in science and research careers among younger students. The Institute supports the Partners in Education Program, which provides students in the Washington, D.C., area with a scientific environment in which they can nurture their interest in the sciences. In FY 2001, NIAID helped establish a 5-year partnership program with Temple University to foster the academic careers of outstanding minority students in middle schools. NIAID's Rocky Mountain Laboratories teamed up with local middle schools and high schools in Montana to present a program that introduces students to biomedical research.

Women's Health

A number of diseases affect women at a disproportionately high rate. Many of these infectious, immunologic, and allergic diseases fall under the mandate of NIAID. The Institute conducts research, either through its own laboratories or through funded mechanisms, on a broad spectrum of these diseases. Virtually all NIAID's clinical studies on HIV/AIDS, autoimmune diseases, chronic fatigue syndrome, and STDs involve women.

HIV/AIDS continues to increase among women worldwide. The Joint United Nations Programme on HIV/AIDS estimated that 18.5 million women were infected with HIV by the end of 2001, accounting for 50 percent of all cases. NIAID researchers are conducting numerous studies of HIV and women and continue to make discoveries that shed light on the nature of HIV infection. NIAID is studying the course of HIV/AIDS disease in women through two cohort studies, WIHS and WITS. Clinical trials to investigate gender-specific differences in disease progression, complications, and/or treatment also are being conducted by the AACTG, the PACTG, and the Community Programs for Clinical Research on AIDS (CPCRA).

Previous research has shown that many factors—including viral load, STDs, alcohol use, crack or cocaine use, history of childhood sexual abuse, and current domestic abuse—are associated with increased risk of heterosexual transmission of HIV. More recently, NIAID-funded researchers in the WIHS found that HIV-infected women with human papilloma virus (HPV) benefited from highly active antiretroviral therapy (HAART); cervical lesions of the women receiving HAART were more likely to improve compared with those of women not receiving HAART.[55] Data from the WIHS study also have been used recently to demonstrate the impact of HAART. WIHS researchers compared the rate of AIDS and death from 1994 to 1996 (pre-HAART) and from 1996 to 1999 (post-HAART) and found substantial drops in both AIDS and deaths from pre-HAART to post-HAART periods.[56] A recent study in the AACTG demonstrated the usefulness of isotretinoin for preventing low-grade cervical dysplasia in HIV-infected women and confirmed that the management of cervical dysplasia (low-grade squamous intraepithelial lesions) in HIV-infected women probably does not need to differ significantly from that of the general population.[57]

Mother-to-infant transmission of HIV—which can occur during pregnancy or childbirth or through breastfeeding—accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective antiretroviral therapies are not available.

According to the Centers for Medicare & Medicaid Services *(http://cms.hhs.gov/hiv)*, of the 18 million women in the United States eligible for Medicaid, approximately 32,000 are infected with HIV; of those, about 3,000 are pregnant. Virtually all new infections in children are transmitted perinatally. Needless to say, as more women of childbearing age become infected, the number of children infected with HIV also is expected to rise. The HPTN and the PACTG, two NIAID-funded clinical research networks, continue to examine various treatment regimens and strategies to prevent mother-to-child transmission of HIV.

NIAID also has taken the lead on tackling another health issue that disproportionately affects women—autoimmune diseases, which include SLE, rheumatoid arthritis, and multiple sclerosis. Although many autoimmune diseases are rare, collectively these chronic diseases afflict 5 to 8 percent of the U.S. population and disproportionately affect women. Specifically, 90 percent of the nearly 2 million Americans diagnosed with (or suspected of having) SLE are women. SLE damages multiple tissues and organs and may affect muscles, skin, joints, and kidneys, as well as the brain and nerves.

An estimated 15 million new cases of STDs occur in the United States each year. Although some STDs (e.g., syphilis) have declined to all-time lows, others (e.g., genital herpes, gonorrhea, and chlamydia) continue to spread through the population, posing a significant public health problem. Since symptoms in women are minor or nonspecific, especially in the early stages, STDs in women sometimes are not diagnosed until late in the disease. STDs that occur during pregnancy also can affect the fetus or newborn. About one-quarter to one-half of women infected with an STD during pregnancy give birth to either premature or low-birthweight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant, which may cause permanent disabilities. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can complicate pregnancy.

NIAID's multidisciplinary research strategy to address the complications of STDs includes basic science, vaccine development, behavioral science, development of topical microbicides, and development of rapid and inexpensive diagnostic tests. As research increasingly connects the risk of HIV transmission to the presence of STDs, NIAID has continued research into the biological, biochemical, and behavioral basis of various STDs, as well as their manifestations and potential treatments. NIAID supports STD research through grants to individual investigators, a variety of research programs, STD Cooperative Research Centers, the Institute's STD Clinical Trials Unit, and NIAID's Topical Microbicides Program projects.

An estimated 3 million new infections of *Chlamydia trachomatis* occur each year. Investigators at NIAID's Rocky Mountain Laboratories are studying the immune response to chlamydial infection and are conducting preclinical testing of candidate vaccines. With frequent noninvasive urine-based screening, NIAID scientists have determined that 4 percent of high-risk youths are infected with chlamydia, and more than 15 percent become reinfected within a 6-month period.

About one in five adults in the United States has genital herpes, but only one-third of those people know they have the virus. Although most genital herpes cases present no symptoms, asymptomatic individuals can transmit herpes simplex virus (HSV) to others, and a pregnant woman infected with HSV can transmit the

virus to her baby. Between 20 and 60 percent of U.S. women of childbearing age have been infected with genital herpes, posing a significant risk of neonatal herpes. NIAID is currently investigating prevention methods, including antiviral drugs, monoclonal antibodies, and vaccines. Because about 45 million to 60 million people in this country have genital herpes, these studies are important to assess the role of antiviral suppressive therapy in decreasing herpes transmission. The evaluation of monoclonal antibodies as part of a concomitant therapeutic regimen for babies with neonatal HSV infection also could help battle the persistent problem of neonatal herpes, which is still a life-threatening infection despite the availability of antiviral therapies. NIAID researchers are focusing on two major viral processes in their efforts to discover new targets for anti-HSV therapies: viral binding and entry into the host cell and viral DNA replication.

At any one time, an estimated 20 million people in the United States have genital human papillomavirus (HPV) infections that can be transmitted to others. Studies show high levels of HPV infection in women, with the highest levels in the younger age groups.

Although sexual activity is the most common way to transmit syphilis, pregnant women with the disease can pass the bacterium to their unborn children, which may cause serious mental and physical problems. NIAID is currently supporting a clinical research protocol examining a single oral dose of therapy for early syphilis.

NIAID's research to develop topical microbicides to kill STD pathogens, including HIV, includes basic research, preclinical product development, and clinical evaluation. The Institute supports six Topical Microbicide Program projects and recently initiated the Microbicide Preclinical Development Program. This year, NIAID also sponsored the third Topical Microbicide Preclinical Workshop to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV.

In all clinical research, including biomedical and behavioral studies, NIAID complies with the 1993 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. Congress mandated the establishment of these guidelines in the NIH Revitalization Act of 1993, and NIAID staff members participated in their development. The guidelines stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects, unless there is a compelling reason that such inclusion would be inappropriate. The guidelines also state that women of childbearing potential should not be routinely excluded from participation in clinical research.

In addition to funding research, NIAID supports conferences, meetings, and workshops. The Institute communicates research results to scientists through workshops and conferences, and medical information to the general public and physicians through its Office of Communications and Public Liaison. Every year, approximately 12,000 people call NIAID for information, and thousands more write for copies of pamphlets and other materials.

SEXUALLY TRANSMITTED DISEASES

Sexually transmitted diseases (STDs) are critical global and national health priorities because of the devastating impact they have on women and infants and their relationship with HIV/AIDS. In the United States, more than 65 million people are living with an incurable STD, and an estimated additional 15 million people become infected with at least one STD each year, approximately one-half of whom contract infections that will affect them for the rest of their lives.[58]

A number of conditions may occur later as a consequence of having STDs, including infertility, tubal pregnancy, cervical cancer, fetal wastage, low birthweight, congenital or perinatal infection, and other chronic conditions such as neurosyphilis. Moreover, substantial biological evidence demonstrates that the presence of other STDs increases the likelihood of both transmitting and acquiring HIV. Recent studies indicate that the more prevalent nonulcerative STDs (chlamydia infection, gonorrhea, bacterial vaginosis, and trichomoniasis) and ulcerative diseases (genital herpes, syphilis, and chancroid) increase the risk of HIV transmission by at least threefold to fivefold.[59]

NIAID supports research for more effective prevention and treatment approaches to control STDs. These approaches include (1) the development and licensure of vaccines, topical microbicides, and treatments for the microbes that cause STDs; (2) understanding the long-term health impact that sexually transmitted pathogens have in various populations; (3) stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and (4) developing better and more rapid diagnostics.

To carry out these activities, NIAID supports a broad STD research portfolio *(www.niaid.nih.gov/dmid/stds)* that addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STD Cooperative Research Centers (CRCs), which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. Another program, the STD Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STDs. The Topical Microbicides Program projects conduct basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of STDs and HIV/AIDS infection.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Haemophilus ducreyi*. NIAID also continued to provide support for databases of genomic and postgenomic information and analysis tools on sexually transmitted pathogens *(www.stdgen.lanl.gov)*. This information has provided new insights into the pathogenesis of numerous STDs and is paving the way for new opportunities to develop diagnostics, drugs, vaccines, and microbicides.

In FY 2002, NIAID continued to support and encourage the development and evaluation of STD diagnostics designed for point-of-care use through the Small Business Innovation Research mechanism. NIAID is also supporting a clinical trial to compare a new oral antibiotic

treatment regimen with the one that is currently recommended for the treatment of primary syphilis. Results from this trial could provide an alternative treatment option.

Topical Microbicides

NIAID continues to focus a great deal of its prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, or films, known as topical microbicides, as a means of protecting against sexual transmission of HIV and other STDs.

Topical microbicides work by killing HIV or other sexually transmitted pathogens or by creating a barrier and blocking their ability to enter or bind with cells. Ideally, microbicides would be unnoticeable, fast acting against HIV and a broad range of other sexually transmitted pathogens, inexpensive, safe for use at least one to two times daily, and easy to store. In addition, microbicides are needed both with and without contraceptive properties so that a woman's reproductive decisions do not affect her risk for HIV/STD infection.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive effort is to support research and development that leads to the identification of safe and effective topical microbicides. The Microbicide Preclinical Development Program, which is sponsored jointly by NIAID and the National Institute of Child Health and Human Development (NICHD), supports the discovery and preclinical development of novel or underexplored HIV microbicides. To date, three awards have been made by NIAID, and three have been made by NICHD. In an effort to foster translational research, which takes promising concepts from early preclinical studies into pilot clinical studies, NICHD and NIAID jointly sponsored a new program this year—the Integrated Preclinical/Clinical Program for HIV Topical Microbicides. Under this program, three awards have been made by NIAID and one by NICHD, all of which focus on iterative preclinical and clinical research for novel microbicide strategies against HIV infection.

A Topical Microbicides Program Project Reverse Site Visit, formerly known as the Topical Microbicide Preclinical Workshop, was held this year to review the progress of the Topical Microbicide Program Projects funded by NIAID.

Another program initiated this year—Innovation Grants in AIDS Research—stimulates new, scientifically challenging, and untested ideas in AIDS research, with a particular focus on microbicide research. Applications were encouraged in several areas of new approaches for microbicides, including viral and cellular processes involved in the transmission, local propagation, and spread of HIV; processes for cervicovaginal and rectal transmission of HIV; improved methods of formulation and delivery; and preclinical systems to test microbicide safety and efficacy. Applications with the highest scientific merit will be funded in FY 2003.

NIAID also supports large-scale *in vitro* screening of potential HIV-transmission-blocking agents through a contract with Southern Research Institute—Frederick, Maryland. Potential microbicides from the private sector and from academic and government sources are tested in several different assays to determine their ability to block HIV transmission from infected T cells to cultures of cells lining the human cervix. In the

past year, 29 unique compounds from outside sponsors and 346 unique compounds from the National Cancer Institute Repository were tested. The colorless or lightly colored compounds with a high therapeutic index are undergoing additional evaluation to assess their potential for development as topical microbicides, to determine whether they cause intravaginal irritation or other adverse effects in experimental animals, and to determine whether they remain stable in the vagina after delivery.

NIAID also has a contract with the University of Washington for microbicide development. During the past year, 11 candidate microbicides were evaluated for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in nonhuman primates. Having been found to be safe in this model, three of these candidates have been tested further for efficacy against chlamydial challenge in the same nonhuman primate model.

Several promising topical microbicide candidates are in various stages of clinical testing. BufferGel® is an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive sexually transmitted pathogens, such as HIV. Results from clinical trials through NIAID's HIV Prevention Trials Network (HPTN) in the United States, India, Thailand, Zimbabwe, and Malawi found it to be safe and well tolerated in uninfected women and men.

The HPTN studies of PRO 2000/5 Gel, a synthetic compound that works by inhibiting HIV entry, were recently completed in the United States and Durban and Johannesburg, South Africa, among sexually active women who were at low risk of HIV infection and in sexually abstinent asymptomatic HIV-infected women. PRO 2000/5 Gel was found to be well tolerated at different concentrations.

Since studies of PRO 2000/5 Gel and BufferGel® have shown that they are both safe and well tolerated, NIAID is planning a phase II/III study to further evaluate their safety, effectiveness, and potential use. Toward that end, a study was conducted in HIV-infected men to determine the acceptability of both products since it is likely that they will be exposed to these products in a phase III trial. Preliminary data indicated that BufferGel® and PRO 2000/5 Gel are both relatively safe in that population. A phase III efficacy and effectiveness trial of BufferGel® and PRO 2000/5 Gel with a phase II safety component is planned to begin in FY 2003 through the HPTN.

NIAID has also initiated two phase I studies of new products: 9-(2-phosphonylmethoxypropyl)-adenine (PMPA), which inhibits HIV replication; and cellulose sulfate, an HIV entry blocker. PMPA gel prevented the infection of female monkeys with simian immunodeficiency virus (SIV), a relative of HIV, when they were exposed to SIV in the vagina. The phase I study will determine the safety and acceptability of PMPA gel for vaginal use among sexually abstinent and active HIV-uninfected and HIV-infected women and their male sexual partners, when relevant. The phase I study of cellulose sulfate will be conducted in collaboration with the CONRAD Global Microbicide Project and will also examine the safety and acceptability of the gel among HIV-infected women and their male sexual partners, when relevant.

A clinical trial of *Lactobacillus crispatus*, a specific bacterial strain that naturally colonizes

the vaginas of many women, was also completed this past year. These bacteria produce chemicals that kill harmful microbes, including those that cause STDs, and have been shown to reduce women's risk of getting gonorrhea, HIV infection, and bacterial vaginosis, a type of vaginal inflammation. Although the initial analysis was not encouraging, a reanalysis predicts that a new product formulation combined with a different treatment regimen may improve results.

A strategic plan detailing NIAID long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials, is under development. A Blue Ribbon Panel of outside experts was convened to review a draft of the plan this year. Their recommendations are currently being addressed, and the final plan will be available in printed form and on NIAID's Web site in 2003.

TRANSPLANTATION

Illnesses such as kidney failure, diabetes, leukemia, end-stage pulmonary disease, and cardiovascular and liver diseases affect millions of Americans. Transplantation of solid organs, tissues, or cells can modify outcomes and lifestyles for patients affected by these diseases. With approximately 78,000 patients listed for transplantation in 2001, only 24,110 solid organ transplants were performed.[60] This figure represents a mere 6-percent increase over the number of transplants performed in 2000. Availability of cadaveric organ donors remains a limiting factor in increasing the number of transplants in the United States. Interestingly, the number of living donors surpassed the number of cadaveric donors in 2001, with 6,081 cadaveric and 6,520 living donors.[61] Advances in transplantation have increased the likelihood of graft acceptance by the recipient's immune system. Today, transplantation procedures are performed using more than 25 different organs and tissues, with first-year graft survival rates often exceeding 80 percent. Despite these successes, two major impediments remain: immune-mediated graft rejection and the critical shortage of donor organs.

Immune-Mediated Graft Rejection

Although advances in immunosuppressive therapies have greatly increased 1-year graft survival rates, long-term graft survival is relatively unchanged. NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad spectrum of research to address immune-mediated graft rejection, including basic research in transplantation immunology, preclinical evaluation of new therapies, and clinical trials of promising therapeutic approaches to improve short- and long-term graft survival. The major goals of DAIT-supported research in transplantation are to understand the pathways whereby the immune system recognizes transplanted organs, tissues, and cells; characterize the cellular and molecular components of acute and chronic graft rejection; evaluate novel therapies for treating rejection and prolonging graft survival in preclinical models; develop and implement strategies for immune tolerance induction; and conduct clinical trials of new therapies to improve graft survival.

Kidney transplantation accounts for 58 percent of all solid-organ transplant procedures and is the preferred therapy for end-stage renal disease (ESRD).[62] To establish and coordinate multicenter clinical trials of new immunosuppressive protocols in kidney transplantation, DAIT established the Cooperative Clinical Trials in Adult Kidney Transplantation (CCTAT) in FY 1991. This program was renewed in FY 1995 and now includes 47 transplant centers throughout the United States. Through the CCTAT, NIAID is supporting a pilot study of kidney transplantation into HIV-positive patients. Although the current antiviral therapy available to HIV-positive patients has significantly increased their life expectancy, a complication of this therapy is kidney toxicity, leading to ESRD. With increased life expectancy, these patients may experience renal failure and can be candidates for kidney transplantation. The objectives of this ongoing study are to determine the safety and efficacy of kidney grafts into HIV-positive patients and determine the interactions between the antirejection and the antiviral therapies. Patient sample and data analysis are proceeding. In FY 1994, DAIT established the Cooperative Clinical Trials in Pediatric Kidney Transplantation (CCTPT) to develop clinical strategies to treat and prevent graft rejection in children and to address the

unique characteristics of the pediatric immune system. Clinical trials within the CCTPT are examining the causes of lower patient and graft survival rates in children versus adults and the effects of immunosuppressive therapy on growth retardation. This program will be renewed in FY 2003.

DAIT established program projects in transplantation immunology to enhance understanding of the processes involved in controlling the immune response and to apply this knowledge in the clinical setting. The goals of this research program are to identify and characterize molecules, cells, and mechanisms involved in graft rejection and to develop therapeutic regimens that facilitate successful transplantation by modulating the immune response. Projects range from basic investigations of the genetics and regulation of the immune system to clinical research projects that define immune factors affecting the success of transplantation. Despite substantial improvements in short-term graft survival, long-term graft survival remains poor, primarily because of chronic rejection. Although chronic rejection presents a fairly uniform clinical picture, little is known about its etiology, including the factors that determine onset and severity, the targets of immune reactivity, and what controls the degree of variability in the rejection process between patients. The Immunopathogenesis of Chronic Graft Rejection program, cosponsored by DAIT and the National Heart, Lung, and Blood Institute, is designed to enhance knowledge of chronic graft dysfunction. This program will (1) enhance our understanding of both the immunologic mechanisms that underlie chronic rejection of solid organs and the patterns of gene expression associated with chronic graft rejection, (2) improve diagnostic criteria to predict rejection, and (3) identify novel approaches for clinical intervention.

In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), DAIT supports the Non-Human Primate Immune Tolerance Cooperative Study Group to evaluate the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2002, this program was renewed and several new research centers were added, which will allow a larger number of novel strategies for immune tolerance to be rigorously evaluated. DAIT supports breeding colonies of rhesus and cynomolgus macaques for the nonhuman primate models for transplantation research.

Improvements in immunosuppressive therapy have dramatically reduced acute rejection and have increased the 1-year graft survival rate for all organ transplants. However, many serious side effects, such as infections and malignancies, are associated with the use of systemic immunosuppressive drugs to prevent graft rejection. Reducing these risks, while improving graft and patient survival, is a priority in transplantation immunology. One very attractive alternative to immunosuppression is to interrupt or modify the immune response to establish specific tolerance to the graft. In FY 1999, DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies in the following clinical areas: autoimmune diseases, asthma and allergic diseases, and rejection of transplanted kidneys and pancreatic islets. The goal of tolerance-inducing therapies is to

reeducate the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity to infectious agents. An important aim of the ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate drugs. The ITN membership includes approximately 80 basic research and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. Since its inception, the ITN has initiated more than 15 clinical protocols, a variety of state-of-the-art core facilities, and about 5 additional studies designed to explore immune mechanisms leading to the development, maintenance, or loss of clinical tolerance. The "Edmonton Protocol," an experimental islet transplantation protocol for patients with hard-to-control type 1 diabetes, is the first clinical trial being conducted by the ITN. This trial will assess the safety and efficacy of this treatment regimen at 10 sites in the United States, Canada, and Western Europe. Results of this international, multicenter trial will establish the "baseline" success rate for islet transplantation and facilitate the development of new ITN trials of tolerogenic approaches for islet transplantation. As of October 2002, 35 patients have received islet cell transplants through this research network and 14 have achieved insulin independence. The ITN is conducting two clinical trials on tolerance induction for kidney transplantation. The first trial is a combined bone marrow/kidney transplant for multiple myeloma patients with end-stage renal disease. The second trial will determine the tolerability of a novel T-cell-depleting, monoclonal antibody for tolerance induction. The ITN also is conducting integrated studies aimed at identifying the underlying immune mechanisms involved in disease progression and therapeutic actions of the treatment regimens.

Histocompatibility and Immunogenetics

In FY 2002, NIAID, with cosponsorship from several NIH Institutes and the JDRF, continued its support of the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that collects and shares data on histocompatibility genes. Histocompatibility genes allow the immune system to respond to specific pathogens, but these genes also play a role in the unwanted immune responses that occur in graft rejection and autoimmune diseases. The IHWG will focus on (1) expanding knowledge of the role of histocompatibility genes in cancer and autoimmune diseases; (2) furthering the understanding of human leukocyte antigen (HLA) diversity in ethnically distinct populations to improve donor matching and graft survival; (3) elucidating the genetic structure of the killer cell immunoglobulin-like receptor (KIR) gene family that plays a critical role in the innate immune response; and (4) improving tissue typing methodologies and reagents to ensure that transplant recipients receive the best-matched donor organs and tissues available. Furthermore, the IHWG is conducting a study to define single nucleotide polymorphisms (SNPs) in a large number of immune response genes that play a role in immune-mediated diseases such as graft rejection and autoimmunity. This project will determine SNP frequencies in various ethnic populations that may then be used as a research tool to better understand and treat immune-mediated diseases that disproportionately affect these populations. For more than 20 years, DAIT has supported efforts to identify and characterize antigens of the major histocompatibility complex (MHC), which are critical in matching organ donors and recipients. Until recently, knowledge about the differences

in the type and frequency of transplant antigens in minority populations has been limited. This lack of knowledge has been a major factor in the relatively poor outcomes of minority transplant recipients compared with Caucasians and has contributed to the lower number of transplants performed in minority populations.

Donor Organ Shortage

In 2001, 24,110 organ transplants were performed in the United States, including 14,184 kidneys, 5,181 livers, 2,202 hearts, 466 pancreata, 1,053 lungs, 27 heart-lung combinations, and 886 kidney-pancreas combinations.[63] Living donors represent a rapidly increasing source of organs for transplantation. In the last decade, living donation has increased by 123 percent in contrast with a 44.5 percent increase in cadaveric donors during this same time.[64]

Despite the success of transplantation programs in this country, there remains a critical shortage of donated organs. The ever-increasing waiting list for transplants has quadrupled in size since 1988 to more than 80,000 patients. In 2001, 6,238 of those patients died while awaiting a transplant. In an effort to address these issues, DAIT supports efforts to increase donation by improving donor registries, which are used to identify potential donors, and through the development and testing of educational interventions. These efforts emphasize the involvement of minority populations, especially African Americans who are at a greater risk of end-stage renal disease than Caucasians.

As another avenue to address the critical shortage of donors, DAIT sponsors studies on xenoplantation as an alternative to living and cadaveric donation. Xenotransplantation, the use of nonhuman organs, tissues, or cells in human transplantation, has been largely unsuccessful because of vigorous immune-mediated rejection. DAIT-supported research focuses on increasing our understanding of the human immune response to antigens present on the surface of organs or tissues from nonhuman species and the development of methods to allow rapid identification and treatment of infectious diseases that might occur by transmission of disease-causing organisms across species.

With each advance in transplantation immunology comes a new set of challenges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy transplant waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.

TUBERCULOSIS

NIAID plays a lead role in the NIH tuberculosis (TB) research program. From 1992 to 2001, NIAID has continued to increase its TB research portfolio. This action is in response to ongoing concern about increasing worldwide case rates and the development of multi-drug-resistant strains of *Mycobacterium tuberculosis*, the pathogen that causes TB. The World Health Organization (WHO) estimates that there are approximately 8 million new cases and 2 million deaths from TB each year, making TB the leading cause of death from a single infectious pathogen worldwide. It kills more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M. tuberculosis*, and 1 in 10 of these individuals will likely develop active TB disease. Moreover, it is estimated that between 2000 and 2020, nearly 1 billion people will be newly infected, 200 million people will get sick, and 35 million people will die from TB if we do not significantly improve our ability to control this disease.[65] NIAID supports a broad TB research program, primarily through its extramural Division of Microbiology and Infectious Diseases (DMID), with particular emphasis on the following areas:

- Basic biology and pathogenesis of *M. tuberculosis*, host-pathogen interaction, and host response to TB in animal models and humans;
- Research into the various stages of TB, including persistent, asymptomatic infection with *M. tuberculosis* (latency), reactivation, and progression to TB;
- Development and testing of vaccines, chemotherapeutics, and diagnostics;
- Development of improved tools for epidemiologic studies; and
- Mycobacterial genomics and postgenomic analyses.

NIAID also supports related whole genome-sequencing efforts, including the sequencing and annotation of genomes of pathogenic mycobacteria, such as *M. tuberculosis* (completed) and *M. avium* (completed), and model organisms, such as *M. smegmatis* (almost completed). To facilitate translation of genomic information to improve our understanding of the basic biology and pathogenesis of mycobacterial diseases and stimulate development of new diagnostic tools, vaccine candidates, and drug therapies, NIAID is cofunding, together with the National Institute of General Medical Sciences (NIGMS), the TB Structural Genomics Consortium, which will determine the 3-dimensional structure of more than 400 *M. tuberculosis* proteins *(www.doe-mbi.ucla.edu/TB)*.

Contracts issued by DMID and the Division of Acquired Immunodeficiency Syndrome (DAIDS) are used to support and promote research in TB covering aspects from basic through translational to applied research. Under contract, NIAID (1) offers *M. tuberculosis*-derived research reagents and animal model screening services for candidate TB vaccines *(www.cvmbs.colostate.edu/microbiology/tb/top.htm)*; (2) offers candidate compound identification and acquisition services and *in vitro* and animal model screening services to evaluate drug candidates *(www.taacf.org)*; (3) provides funding for the development of improved TB vaccines using already existing technology platforms; (4) supports the Tuberculosis Research Unit (TBRU) to conduct multidisciplinary

laboratory and clinical studies to answer critical questions in human TB; to provide knowledge, tools, and technologies to improve human clinical trials in TB; and to provide the ability to conduct clinical studies for the evaluation of new or improved vaccines, therapeutics, and diagnostics *(www.tbresearchunit.org)*; and (5) assists with technology transfer for potential commercialization of new drug discoveries for TB.

NIAID has established a chemical database to serve as a reference for TB drug-screening results and to stimulate the design and synthesis of new candidate drugs. A clinical trials network is evaluating existing drugs approved for other clinical indications, and the National Cooperative Drug Discovery Groups—Opportunistic Infections is searching for new drug targets and candidate lead compounds against *M. tuberculosis*. NIAID also participates in a newly formed public-private partnership—the Global Alliance for Tuberculosis Drug Development—together with WHO, the Rockefeller Foundation, and other international organizations dedicated to encouraging new therapeutic advances in the absence of industrial sponsorship. Increased funding through Small Business Innovation Research grants has promoted development and evaluation of new diagnostic tests for *M. tuberculosis*.

The Division of Allergy, Immunology and Transplantation (DAIT) supports a number of individual research projects concerned with basic mechanisms of immunity to *M. tuberculosis*. DAIT's research goals and objectives on *M. tuberculosis* are to:

- Understand how the immune system recognizes and responds to bacteria hidden within host cells, such as *M. tuberculosis*, and encourage research on antigen presentation and stress molecule induction as they relate to activation of cell-mediated immunity to intracellular pathogens;
- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;
- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and
- Support research on the identification of genes expressed in immune responses to mycobacterial infection, especially soluble proteins that might be used in vaccination or in treatment of the disease.

Research topics include T-lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating M. tuberculosis infection, and the function of biological oxidants in protective immune processes.

DAIT supports several projects that focus on hepatitis C, TB, malaria, and HIV. Under the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines program, DAIT also supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and self-proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs that will facilitate their research efforts.

Support is provided under a NIAID contract to the University of Oklahoma. The Web address is *http://hlaligand.ouhsc.edu*.

The NIAID Tetramer Facility produces peptide-MHC reagents for T-cell detection and has provided more than 750 tetramers to investigators worldwide. Requests include reagents for the study of T-cell responses relevant to many vaccine topics, including intracellular bacterial, viral, and parasite infections, autoimmune diseases, and basic immunobiology. More information on this facility can be found at *www.niaid.nih.gov/reposit/tetramer/index.html*. The National Cancer Institute also provides funding for the Tetramer Facility.

The Division of Intramural Research (DIR) has a substantial intramural program that integrates genomics and combinatorial chemistry to speed development of new antibiotics for the control of tuberculosis. After contributing to the determination of the genomic sequence of *M. tuberculosis*, DIR investigators are now focusing on unraveling the functions of its various genes. This knowledge is critical to new drug and vaccine development and to understanding the molecular mechanisms involved in the emergence of drug resistance.

DIR scientists also are working on a number of different approaches to understand how current antitubercular chemotherapy works. They will use this information to develop new and improved therapies and therapeutic approaches. Individual projects are aimed at understanding the mode of action of existing front-line antituberculars, such as isoniazid and ethambutol, two drugs that form the backbone of modern short-course chemotherapy for TB. This knowledge is translated into screens for second-generation antituberculars based on the same basic mechanism of action.

DIR tuberculosis research efforts include several collaborations with extramural partners. One such partnership with scientists from PathoGenesis Corporation uncovered the mechanism of action of the nitroimidazopyrans, the first new class of antibiotics advanced for preclinical consideration in more than 30 years. The compounds were shown to have significant activity against bacteria that are not actively replicating, a finding that has important implications for the one-third of the world's population that harbors latent bacilli and is at continued risk for the development of active TB.

Another important collaboration with colleagues from GlaxoSmithKline (GSK) and St. Jude's Children's Hospital aims to develop novel antituberculosis drugs based on thiolactomycin, a compound isolated from a soil bacterium. All of the new drug candidates are being synthesized at NIH, tested at GSK, and co-crystallized with the target enzyme at St. Jude's. This partnership between a large pharmaceutical company, Government, and academic laboratories is a model for the development of drugs against diseases that lack the financial impact necessary to attract independent attention from the global pharmaceutical industry.

NIAID's increased support for TB research has resulted in significant advances in our understanding of the basic biology, microbiology, and immunology of TB, which will result in the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.

VACCINE RESEARCH AND DEVELOPMENT

Vaccines are a safe, effective, and efficient means of preventing morbidity and mortality from infectious diseases. NIAID is the center of vaccine research and development within the Department of Health and Human Services. The Institute's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nurtured comprehensive, collaborative vaccine efforts among scientists in Government, industry, and academic institutions. In setting priorities for vaccine development, NIAID weighs the severity of disease and expected health benefits, considers the scientific and programmatic gaps and opportunities, and studies the feasibility, given the status of scientific knowledge about particular diseases and their causative agents.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) supports the discovery and development of safe and effective vaccines to prevent HIV infection and AIDS worldwide. Toward this end, DAIDS has a comprehensive portfolio of research grants and programs spanning basic vaccine research and preclinical testing of candidate HIV vaccines, through human clinical testing in the United States and internationally.

The Division of Microbiology and Infectious Diseases (DMID) also supports a full spectrum of vaccine research to (1) prevent infectious diseases, such as tuberculosis (TB), malaria, cytomegalovirus (CMV), group B streptococcus, and chlamydial infections; (2) serve fragile populations, such as infants, older people, and immunocompromised people; (3) evaluate novel vaccine approaches, such as oral, transcutaneous, and combination vaccines; and (4) improve existing vaccines.

Both DAIDS and DMID support large clinical networks and have vaccine production contracts that provide opportunities to develop and advance vaccine concepts into early stages of clinical evaluation. Infrastructure for regulatory oversight, site monitoring, and data management round out the vaccine development process. In collaboration with the Fogarty International Center, both Divisions support capacity building and training in clinical research.

Research supported by NIAID's Division of Allergy, Immunology and Transplantation (DAIT) is designed to apply the fundamental principles of immunology to the development of improved vaccines. NIAID's Division of Intramural Research (DIR) conducts a wide-ranging vaccine program. Extensive efforts are under way to develop vaccines to prevent diseases of worldwide importance, such as malaria, AIDS, childhood respiratory infections, chlamydia, hepatitis C and E, Lyme disease, dengue fever, rabies, and genital herpes. The Institute's Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease, with the primary focus of research being the development of vaccines for AIDS.

Division of Acquired Immunodeficiency Syndrome

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic. Although educational and counseling efforts have had some success and remain essential, these prevention activities alone will not be sufficient to contain the worldwide spread of disease. An HIV vaccine represents the best hope for controlling the HIV epidemic.

The NIH has several significant resources devoted to the development of safe and effective HIV vaccines. The AIDS Vaccine Research Working Group (AVRWG), the VRC, and NIAID's comprehensive HIV vaccine research program are key to advancing HIV vaccine research. The AVRWG, chaired by Dr. Barton Haynes, stimulates HIV vaccine research and assists the NIH in developing a comprehensive research program aimed at expediting the discovery and development of a safe and effective vaccine. Serving as a focal point for intramural scientists at the NIH, the VRC advances multidisciplinary research from basic and clinical immunology and virology to vaccine design and early clinical testing. This work complements the comprehensive extramural research activities of DAIDS.

DAIDS supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages of concept genesis and evaluation through the Innovation Grants for AIDS Research Program, and basic vaccine research and design, including testing in animal models, mechanism-of-action studies, and studies of immune correlates through the HIV Vaccine Research and Design Program. In the past year, innovation grants were awarded to researchers who are investigating virus vector vaccine designs, T-cell immunology, animal model development, and DNA vaccines. The HIV Vaccine Research and Design Program supported research in the area of multicomponent HIV vaccines using engineered envelopes, HIV vaccines based on serotypes of adenovirus, and structural approaches to vaccine development. The Integrated Preclinical/Clinical Vaccine Development Program, which targets research at the preclinical-clinical interface of the vaccine research pipeline, made an award this year to further HIV vaccines designed to induce mucosal immunity. The New Technologies for HIV and HIV Vaccine-Related Research Program supports the use of novel and innovative technologies to detect and quantitate HIV, optimize measurement of immune responses to HIV and candidate HIV vaccines, and evaluate and quantitate immune responses responsible for the efficacy of licensed vaccines for other infectious diseases. In the past year, awards through this program were made to standardize measurements of HIV-specific CD8+ T cells, examine the role of gamma-delta T cells in vaccine-induced immunity, and explore novel biological activities of antiviral antibodies.

To help expedite the development of promising HIV/AIDS vaccines, DAIDS also has several novel public-private partnerships under a program titled the HIV Vaccine Design and Development Teams (HVDDT). These "teams" tap the different skills and talents of private industry and academic research centers and are given financial incentives to move strong HIV/AIDS vaccine candidates out of the laboratory and into human testing. The HVDDT program responds to the need to increase public-private cooperation in developing HIV vaccines and malaria, and encourages pharmaceutical companies to invest more in AIDS vaccine research by partially offsetting their financial risk. Before this year, HVDDT contracts resulted in progress toward the development of several clade B (the most prevalent subtype of HIV in the Americas and Europe), clade C (the most prevalent subtype of HIV in Africa and Southeast Asia), and multiclade vaccine candidates. Many of these products will be ready for human clinical trial testing in 2003. An additional award was made this past year for the development of vaccine candidates based on vesicular stomatitis virus vectors, which have been effective in inducing

strong cellular and antibody responses in animal models.[66]

Clinical HIV vaccine research is carried out through the HIV Vaccine Trials Network (HVTN), a global HIV vaccine research network, which was established in 2000 to foster the development of HIV vaccines through testing and evaluating candidate vaccines in clinical trials. The network has the capacity to conduct all phases of clinical research, from evaluating candidate vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. HVTN sites are located in Botswana, Brazil, China, the Dominican Republic, Haiti, India, Peru, South Africa, Thailand, Trinidad, and the United States. Site expansion is currently under way in Botswana, Malawi, and South Africa. In addition, new international sites have been identified in the Caribbean (the Dominican Republic and Puerto Rico) and Central America (Honduras) that will further expand HVTN capacity. (See page 15 for a map showing the HVTN sites.)

NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) of the Department of Defense also have been working closely to ensure the effective integration and coordination of HIV vaccine research efforts. NIAID and the USAMRMC share a common goal—to prevent the further spread of HIV/AIDS by developing safe and effective vaccines, other prevention strategies, and innovative HIV treatments—and both agencies are committed to maintaining and building on each other's strengths. The merger of the two programs will ensure that U.S. Government HIV vaccine research is well coordinated, efficient, and comprehensive.

To date, NIAID has supported more than 61 HIV phase I and phase II vaccine trials, involving well over 4,088 volunteers. A total of 32 candidate vaccines and 13 different adjuvants (a substance that enhances the immune-stimulating properties of a vaccine) have been tested with 1 or more of 10 routes or methods of administration.

NIAID research has demonstrated that the use of a combination vaccine approach is safe and immunogenic in volunteers at both low and high risk for HIV infection. This approach has been shown to stimulate cellular immunity, resulting in cytotoxic T lymphocytes (CTLs) that can kill infected cells, and in the production of HIV-neutralizing antibodies that can stop HIV from infecting cells. Thus, the combination approach holds promise because it stimulates production of HIV-neutralizing antibodies and cellular immunity.

Plans are currently under way for NIAID to support the USAMRMC-sponsored phase III prime-boost vaccine efficacy trial that is being planned in partnership with the Thai government and Thai researchers. The study will test a combination of a canarypox vaccine followed by a gp120 subunit booster vaccine. The canarypox-HIV vaccine is made up of a weakened canarypox virus that has been genetically altered to contain selected HIV genes. Neither the canarypox nor the gp120 subunit vaccine can cause HIV infection. The phase III trial in Thailand is expected to commence in 2003.

Several other NIAID HIV vaccine studies involving the prime-boost approach are under way. Other studies that have been initiated recently include a study to evaluate the safety and immunogenicity of a vaccine involving a NefTat fusion protein in combination with varying doses of gp120 and two new epidemiologic and observational studies. These studies will evaluate the HIV immunologic

response and viral characteristics of vaccine volunteers who acquire HIV after enrolling in HIV vaccine studies, and international recruitment and retention strategies for high-risk individuals for phase III trials.

Future safety and immunogenecity trials will involve lipopeptides, an alphavirus replicon HIV subtype C gag HIV vaccine (AVX101), a recombinant adenovirus HIV vaccine, and novel HIV DNA vaccines with or without novel adjuvants. DNA vaccines and viral vectors incorporate HIV genes to produce specific HIV proteins that then induce an immune response.

Preclinical research advanced our knowledge about viral escape from CTLs. Although several studies have shown that CTLs are important in controlling HIV, a recent finding showed that viruses containing a single mutation could no longer be controlled by CTLs and could replicate enough to cause disease. This finding emphasizes the need to develop a vaccine that elicits the greatest breadth of CTL and antibody responses possible so that CTL recognition at one site will not allow the virus to replicate.[67]

Division of Microbiology and Infectious Diseases

Because vaccines can provide a safe, effective, and efficient means to prevent illness, disability, and death from infectious diseases, research leading to new and improved vaccines is a high priority for DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve the health of the Nation. Factors that influence priorities for vaccine research include the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, and recommendations made by the National Vaccine Advisory Committee and other advisory groups. DMID designs and implements a comprehensive research program to develop new or improved vaccines that will prevent or reduce the incidence of such infections in susceptible populations. Advances in the fields of microbiology, immunology, and biotechnology are applied to the development of new vaccines and to the improvement of existing vaccines through research support on the following:

- New vaccines against major diseases caused by respiratory syncytial virus (RSV), malaria, group A and group B streptococci, and other bacterial, parasitic, and fungal infections of both children and adults;
- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections, such as group B streptococcus, and congenital diseases caused by CMV infection, toxoplasmosis, syphilis, gonorrhea, and chlamydia infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori* and drug-resistant bacteria such as pneumococcus; and
- Novel technologies to enhance the effectiveness of vaccines, such as adjuvants, proteosomes, and plasmid DNA approaches.

Spurred on by advances in the basic sciences, new vaccine candidates continue to be developed. Vaccines of high public health relevance, often developed in collaboration with industry, are tested for safety and efficacy in preclinical studies. If they remain promising, they may be evaluated in the DMID Vaccine Evaluation Network, which includes the Vaccine and Treatment Evaluation Units (VTEUs) and other units at universities across the United States. An integral part of NIAID vaccine research efforts, these vaccine units support carefully planned and designed clinical trials of novel bacterial, parasitic, and viral vaccines and other biologics in people of all ages and risk categories. In FY 2002, NIAID awarded new contracts for VTEUs and several other vaccine units, expanding and reorganizing the Institute's network of university-based sites that conduct clinical trials of promising vaccine candidates and therapies for infectious diseases. This reconfigured network will enable NIAID to fund more clinical trials focused on specific populations as well as larger trials of public health importance, including those related to biodefense and vaccine safety.

In addition, the evaluation of vaccine safety is an integral component of the NIAID vaccine research program. Safety is evaluated in every vaccine clinical trial sponsored by NIAID. Study participants are monitored closely for any adverse effects of the vaccinations they receive. Specific safety issues, such as the use of novel cell substrates for vaccine development and the evaluation of combination vaccines, are explored through scientific consultation with other Federal agencies and in coordination with the National Vaccine Program Office (NVPO).

DMID also supports research to develop new approaches for the following:

- Generating long-lasting protective immunity against various infectious agents;
- Favoring the development of mucosal immunity or the production of an antibody of a given isotype;
- Increasing the immunogenicity of candidate vaccines or favoring the expression of a cell-mediated cytotoxic immune response; and
- Simplifying immunization regimens to reduce the number of immunizations required for protection and the number of visits to health care facilities and associated costs.

With an integrated and comprehensive research program in infectious diseases, microbiology, and immunology, NIAID is prepared to lead research efforts on the development of safe and effective vaccines for the prevention of a variety of infectious diseases. Thus, DMID is recognized as an effective participant in U.S. national vaccine policy. In the United States, NIAID collaborates with other vaccine agencies, including the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration, on issues of vaccine research, vaccine safety, and national immunization strategies, coordinated through the NVPO.

Internationally, DMID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization (GAVI) and the Multilateral Initiative on Malaria (MIM). GAVI was established in 1999 as an alliance of global partners to replace the Children's Vaccine Initiative. This global alliance has the support and participation of

international agencies (e.g., the World Health Organization, UNICEF, and the World Bank) as well as bilaterals, industry, nongovernment agencies, and foundations. The creation of the Global Alliance has been accompanied by significant financial commitments from the Bill and Melinda Gates Children's Vaccine Program. The mission of GAVI is to save children's lives and protect people's health through the widespread use of safe vaccines, in the belief that every child, regardless of place of birth or socioeconomic status, should be protected against vaccine-preventable diseases of public health priority.

NIAID, in collaboration with CDC, requested that IOM establish an independent expert committee to review hypotheses regarding the relationship between specific vaccines and alleged adverse events. In response, IOM created the Immunization Safety Review Committee in September 2000. This committee reviews the state of knowledge regarding a specific immunization safety concern and communicates its results to providers and the public. In the past 2 years, the committee has met to review several important vaccine safety issues, including measles-mumps-rubella vaccine and autism, thimerosal-containing vaccines and neurodevelopmental disorders, multiple immunizations and immune dysfunction, hepatitis vaccine and neurological disorders, and SV40 contamination of polio vaccine and cancer. Within several months of each meeting, the committee publishes a report to disseminate its findings, including recommendations for any additional actions (e.g., research or surveillance) that are needed to better understand these safety issues.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. These applications include the following:

- Use of recombinant DNA technology for the production of defined immunogens as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate immune response in selected host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce health care costs and the number of visits to health care facilities.

Division of Allergy, Immunology and Transplantation

DAIT supports research on immunologic mechanisms and novel technologies applicable to vaccine design and development. The Division funds vaccine-related research projects on innate and adaptive immunity that aim to increase our ability to rationally manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Projects include basic studies of innate immune receptors for pathogen molecules, antigen processing and presentation, the development of antibody and cellular responses, and the elaboration of immunologic memory. Other topics more immediate to vaccine applications include the development of new adjuvants to enhance

immunity, the design of approaches to induce protection in mucosal tissues, and the discovery of novel methods for more effective delivery of immunizing agents.

DAIT continues to fund four Vaccine Immunology Basic Research Centers that focus on the fundamental aspects of human protective immune mechanisms in infectious diseases. Through the Human Immunology Centers of Excellence Program, DAIT supports numerous mechanistic studies that will contribute to our basic understanding of human immunity and vaccine responses.

In FY 2002, the Hyperaccelerated Award/Mechanisms in Immunomodulation Trials research program was expanded to support the study of immunologic mechanisms in clinical trials of vaccines, particularly studies of human immunologic function in vaccination, including analyses of the underlying mechanisms of protective immunity, specificity and kinetics of immune responses, and immune memory. Proposed studies must make use of clinical samples from a parent clinical trial that is supported by other funding.

DAIT established the program on the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines and supports several projects within the program that focus on hepatitis C, TB, malaria, and HIV. In this program, investigators tested systematic molecular modifications of natural antigenic peptides—protein fragments that are recognized by specific T cells—and found that certain types of alterations resulted in peptides that were more effectively recognized than the original. In some cases, more than a millionfold less modified peptide was needed to obtain the same response as compared with the original peptide. When used to immunize mice, the modified peptides efficiently elicited cytotoxic T cells that were still able to recognize the original peptide. These observations suggest that systematic molecular alterations of peptides may be an advantageous approach for designing vaccines for better cytotoxic T-cell responses. Also under this program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and self-proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs. Support is provided under a NIAID contract with the University of Oklahoma. The Web address is *http://hlaligand.ouhsc.edu*.

An important new area of disease prevention focuses on the use of vaccination approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease exists, development appears to be feasible based on studies in animal models. Vaccines for autoimmune diseases will be distinct from vaccines given to prevent infectious diseases. Vaccines for autoimmune diseases will "turn off" a destructive immune response that is directed at the body's own tissues. NIAID, in collaboration with multiple NIH Institutes and the Juvenile Diabetes Research Foundation International, awarded five cooperative agreements in FY 2001 to focus on development of the knowledge necessary to rationally design and implement strategies to prevent autoimmune diseases, including type 1 diabetes.

The NIAID Tetramer Facility produces MHC/peptide reagents for T-cell detection and has provided more than 1,400 tetramers to investigators worldwide. Reagents are provided for the study of T-cell responses relevant to vaccine research and development for many diseases, including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at *www.niaid.nih.gov/reposit /tetramer/index.html*. The National Cancer Institute also provides funding for the Tetramer Facility.

Division of Intramural Research

The Division of Intramural Research (DIR) is working to develop vaccines against many infectious agents of public health importance, including respiratory and gastrointestinal viruses, hepatitis viruses, West Nile virus, and infectious agents that cause common tropical diseases such as malaria and dengue. For example, a hepatitis A vaccine that was developed in one of the DIR laboratories has been licensed, and a second hepatitis vaccine, against hepatitis E, is currently in clinical trials in Asia. Candidate vaccines for pandemic influenza, parainfluenza, respiratory syncytial virus (RSV), and the newly discovered RSV-like human metapneumoviruses are tested for safety, immunogenicity, genetic stability, and efficacy at the DIR-supported VTEUs. Each year about 10 candidate vaccines are evaluated at the Johns Hopkins University VTEU.

DIR scientists have developed a needle-free vaccine that targets the two most important viral agents of pediatric respiratory tract disease worldwide, RSV and human parainfluenza type 3 (HPIV3). DIR researchers and colleagues constructed the vaccine by adding key HPIV3 and RSV genes to a genetically modified form of parainfluenza virus from cows. The cow virus was used because it can stimulate immunity in people but does not cause disease. When the vaccine was given intranasally to rhesus monkeys, it stimulated strong RSV- and HPIV3-specific immune responses in those animals. This work presents a novel vaccine strategy that overcomes many of the deficiencies seen with earlier attempts to produce vaccines against these viruses.[68]

DIR researchers also are working to improve the current licensed hepatitis A vaccine (made from killed virus), which requires multiple booster shots to be given intramuscularly—an expense and inconvenience that inhibits its use in less developed countries. The scientists are attempting to develop a live hepatitis A vaccine made from a deliberately weakened form of the virus that could be given orally in a single dose. Their studies have revealed the genes responsible for hepatitis A virulence, but in experiments in which these genes were mutated to weaken the virus, the virus often reverted to its more virulent form. Studies are ongoing to determine the feasibility of this live oral vaccine approach.[69]

DIR scientists and CDC colleagues made an important finding that may bring us closer to a vaccine for malaria. Post-infection immunity to malaria often correlates with the presence of antibodies to a particular protein produced by the malaria parasite. This protein helps infected red blood cells stick to blood vessel walls, enabling the parasite inside to avoid being cleared by the spleen. The scientists took a fragment of the protein required for cell adherence and used it to immunize monkeys. Because the fragment represents the working part of the protein, the researchers proposed it was not amenable to extensive variation and therefore might work in a broadly active

vaccine. The injected fragment protected the monkeys from infection even when variant forms of the protein appeared. This work suggests a promising new approach to malaria vaccine development.[70]

Dengue is an emerging mosquito-borne viral infection that causes an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of potentially fatal dengue hemorrhagic fever each year. DIR scientists conducted phase I testing of a live-attenuated dengue type 4 vaccine candidate derived using recombinant DNA technology and found it was safe and immunogenic, but retained mild liver virulence evident by increased levels of alanine aminotransferase (ALT) in some volunteers. An increase in ALT levels is an indication of a mild liver abnormality seen in some patients. Researchers are continuing to investigate methods for further weakening the dengue type 4 vaccine, which can serve as a basis for creating a vaccine that protects against all four types of dengue virus.[71] Vaccines also are being developed for other mosquito-borne and tick-borne viruses, including West Nile and St. Louis encephalitis viruses, both of which are widely disseminated throughout the United States, and tick-borne encephalitis virus, which is widely disseminated throughout the northern hemisphere.

Traditionally, identification of potential new vaccine candidates has been a slow and laborious process conducted one gene or protein at a time. However, genome sequencing and other high-throughput analytic techniques now provide far more rapid and efficient methods to identify parts of an infectious agent that can be studied for their suitability as potential human vaccines. DIR scientists are using these modern tools to identify potential vaccine components for group A streptococcus, *Mycobacterum tuberculosis*, and other agents that cause significant morbidity and mortality worldwide.

Vaccine Research Center

The Dale and Betty Bumpers VRC is dedicated to improving global human health through the rigorous pursuit of effective vaccines for human diseases. Established by former President Bill Clinton as part of an initiative to develop an AIDS vaccine, the VRC is a unique venture within the NIH intramural research program. The role of the VRC is to stimulate multidisciplinary research and fill the gap between new basic concepts in immunology and initiation of clinical trials through the application of state-of-the-art methods to rational vaccine design. Late in the summer of 2000, construction of the VRC was completed, and newly recruited scientists began moving into their laboratories.

This year, the VRC initiated a clinical trial testing the first AIDS vaccine invented at the new facility. This HIV DNA vaccine contains the DNA blueprint for two pieces of HIV: "gag," which is HIV's core protein, and "pol," which includes three enzymes crucial for HIV replication. Once inside the body, the DNA in the vaccine instructs certain cells to make small amounts of these HIV proteins. Because the vaccine does not contain genetic material for the whole virus, it cannot cause HIV infection. The study will enroll 21 healthy men and women to determine whether the vaccine is safe and whether the body makes an immune response to these proteins.

The construction of the Vaccine Development Facility (VDF) is a high priority for the VRC. The VDF will manage production of multiple vaccine candidates originating from the VRC. To achieve this objective, the VDF will function

in concert with the Vaccine Production Laboratory located at the Bethesda campus in transferring new vaccine technology for pilot-scale production of clinical trial material.

NIAID-SUPPORTED REPOSITORIES

NIAID's intramural and extramural researchers have developed an ample supply of resources and reagents that are used by scientists worldwide for basic research, applied research to develop therapeutics and vaccines, and commercialization. These resources include peptides, cell lines, monoclonal antibodies, viral vectors, and animal models.

Division of Acquired Immunodeficiency Syndrome

Biological Reagents and Reference Standards

The AIDS Research and Reference Reagent Program acquires and distributes state-of-the-art reagents for AIDS-related research and makes these reagents available to qualified investigators throughout the world. It has grown significantly during the past 14 years and now has more than 4,300 reagents for public distribution. The AIDS Research and Reference Reagent Program also encourages and facilitates technology transfer through workshops, publication of methods, and provision of standardized panels and protocols; facilitates commercial development of reagents; and participates as an AIDS Collaborating Center of the World Health Organization (WHO). Additional information is available at *www.aidsreagent.org.*

Through the Vaccine Reagent Resource, the Division of Acquired Immunodeficiency Syndrome (DAIDS) also provides resources for the production or procurement of reagents essential for vaccine studies conducted by the HIV Vaccine Trials Network (HVTN) and the Simian Vaccine Evaluation Units (SVEUs), as well as other priority vaccine studies. These resources also provide for the quality assurance testing of reagents. Additional information is available at *www.niaid.nih.gov/daids/vaccine/reagentres.htm.*

Human HIV Specimens

Research on HIV transmission and disease progression patterns greatly benefits from a centralized system for receiving, cataloging, storing, and distributing samples collected from various well-characterized cohorts of HIV-infected individuals. NIAID provides state-of-the-art storage and computerized inventory management of specimens from domestic and international HIV epidemiology studies, HIV therapeutic and vaccine trials, and other prevention research studies through its central repositories. The reagent program has immortalized and expanded white blood cells from more than 7,000 specimens from DAIDS-supported cohort studies of HIV-infected people, including the Multicenter AIDS Cohort Study (MACS), Women's Interagency HIV Study (WIHS), and Women and Infants Transmission Study (WITS). These preserved cells will provide a source of DNA for future studies of genetic factors in HIV disease. By making these specimens available to the scientific community, DAIDS fosters collaboration among scientific investigators to promote further progress in the detection, treatment, and prevention of HIV disease. To date, more than 2,000 scientists in the United States and 63 countries have been registered to receive reagents and more than 140,000 vials of reagents have been distributed.

The reagent program contract was amended this year to jump-start acquisition and distribution of urgently needed quality-controlled reagents for research on biodefense and emerging infectious disease agents, such as anthrax, transmissible spongiform encephalopathies (TSEs), and hepatitis C virus (HCV). The

program is already in the process of acquiring recombinant anthrax proteins, including protective antigen (PA), lethal factor (LF), edema factor (EF) and monoclonal antibodies for these proteins.

Division of Allergy, Immunology and Transplantation

Multiple Autoimmune Disease Genetics Consortium (MADGC)

Different autoimmune diseases are often found within a single family, suggesting common genetic contributions to the diseases. MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides well-characterized materials for use in research aimed at identifying the genes involved in autoimmune diseases. MADGC began enrolling families in May 2000. To date, 102 families have been fully enrolled and 123 families are in the process, working toward the goal of 400 families in 2004. More information can be found at *www.madgc.org.*

North American Rheumatoid Arthritis Consortium (NARAC)

NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. More information can be found at *www.medicine.ucsf.edu/rheum/narac/nfnarac.htm.* This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation.

Primary Immunodeficiency Diseases Registry (PIDR)

This registry was established by NIAID through a contract with the Immune Deficiency Foundation (IDF) to maintain clinical information on patients in the United States affected by primary immunodeficiency diseases. For each disease, the registry collects information on the natural course of the disease, including early and late complications, effects of therapy, and causes of death. The diseases included in the registry are chronic granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease (SCID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte-adhesion deficiency, and DiGeorge syndrome. Researchers may apply to the registry to obtain access to the patients for both basic research studies and clinical trials.

National MHC Tetramer Core Facility

In FY 1998, NIAID established a contract facility to provide researchers with peptide-major histocompatibility complex (MHC) tetrameric molecules for analyzing antigen-specific T-cell responses. Because T cells are central to virtually all immune responses, this technology is applicable to studies in many areas, including basic immune mechanisms, infectious diseases, vaccination, autoimmunity, transplant rejection, and tumor therapy. By centralizing the production of these tetramers, individual, defined peptide-MHC molecules can be produced economically and can be made available to investigators at greatly reduced expense.

The MHC tetramer core facility is located at

Emory University in Atlanta, Georgia, under the direction of Dr. John Altman.

Division of Intramural Research

Transgenic and Gene-Targeted Mice Repository

The Division of Intramural Research (DIR), in collaboration with the Division of Allergy, Immunology and Transplantation (DAIT), supports facilities for the acquisition, breeding, and distribution of transgenic and gene-targeted (knockout) mice, which are mice that are genetically engineered to serve as animal models for human diseases that do not occur in nonhuman species. The repository provides these mice to both intramural and extramural investigators through the NIAID/Taconic exchange programs for use in research and for development of clinical therapies in various infectious and immunologic diseases.

Division of Microbiology and Infectious Diseases

Leprosy Research Support and Armadillo Colony Maintenance

Although the prevalence of leprosy has declined significantly because of multidrug therapy, leprosy remains a problem worldwide. A major obstacle to leprosy research, however, is the difficulty in culturing *Mycobacterium leprae*, the organism responsible for leprosy. To overcome this problem, the Division of Microbiology and Infectious Diseases (DMID) supports the maintenance of an armadillo colony, the best animal model system of *M. leprae* infection. DMID also funds a repository of viable *M. leprae* and purified, defined reagents derived from *M. leprae*, which are available to researchers worldwide.

Parasitic Disease Research Support

DMID supports three research repositories that supply parasitic organisms whose life cycles are typically too costly or too difficult for investigators to maintain in their own laboratories.

Schistosomiasis and Filariasis Research Repositories. The schistosomiasis repository provides qualified requesters with rodent-definitive hosts and with snail intermediate hosts infected with *Schistosoma mansoni, S. japonicum*, and *S. haematobium*. The filariasis repository provides rodent-definitive hosts and mosquito intermediate hosts infected with *Brugia malayi*, *B. pahangi*, or *Dirofilaria immitis*. Organisms are provided free of charge, except for shipping costs, to both NIH-supported and independent investigators.

Malaria Research and Reference Reagent Repository. The malaria repository has been established to acquire, produce, and distribute malaria research reagents, reference materials, and other information to qualified investigators throughout the world. A major component of the program is the quality control of reagents, standardization of protocols, and exploration of new technologies. International workshops and training sessions will be organized to stimulate and support both laboratory-based and field-based research. The long-term goal of the repository program is to promote technology transfer as well as to facilitate research leading to commercial development of reagents for malaria diagnostics, prevention, and treatment. NIAID has established the repository in support of the Multilateral Initiative on Malaria, a research capacity-strengthening program in partnership with other national and international organizations.

Pneumococcal Reference Laboratory

This laboratory provides reference and resource services and expertise to facilitate the evaluation of improved pneumococcal vaccine. A major objective is to establish a consensus assay and to improve and modify procedures for measuring antibody activity to pneumococci. The laboratory also provides radiolabeled polyribosylribose phosphate (PRP) and/or suitably derivatized PRP and purified PRP to laboratories for the performance of *Haemophilus influenzae* type b assays and for calibration of immunodiagnostic assays.

Repository for Biological Reagents and Reference Standards

This repository stores and distributes serological and microbiological reagents for use as reference standards and for research in infectious and immunologic diseases. As a WHO Collaborating Center for Antiviral Drugs and Interferon, this NIAID repository is responsible for the storage and worldwide distribution of WHO international interferon standards and reference reagents.

Tuberculosis Research Materials and Vaccine Testing

Mycobacterium tuberculosis, the organism responsible for tuberculosis (TB), is difficult and time-consuming to grow and, because it is transmitted via aerosols, should be studied only in appropriate biohazard facilities. DMID funds a repository to provide *M. tuberculosis*-derived materials to qualified TB investigators worldwide in basic and clinical research areas, allowing work to begin quickly and eliminating the need for these investigators to have their own biohazard facilities. DMID also supports the screening of potential anti-TB vaccine candidates, which are provided by individual researchers, in established small-animal, low-dose, aerosol-challenge models.

REFERENCES

1. UNAIDS and World Health Organization (WHO). AIDS *epidemic update*, December 2001. *www.unaids.org/epidemic_update/report_dec01/index.html#full*.
2. Centers for Disease Control and Prevention (CDC). *HIV/AIDS surveillance report*, December 2000.
3. Dybul M et al. Short cycle intermittent highly active antiretroviral therapy for the treatment of chronic HIV infection: effects on virologic, immunologic, and toxicity parameters. *Proc Natl Acad Sci USA* 2001;98:15161-15166.
4. Miller KD et al. Immunotherapy of HIV-infected patients with intermittent interleukin-2: effects of cycle frequency and cycle duration on degree of CD4(+) T-lymphocyte expansion. *J Clin Immunol* 2001;99:30-42.
5. Arthos J et al. Biochemical and biological characterization of a dodecameric CD4-Ig fusion protein. *J Bio Chem* 2002;277:11456-11464.
6. Fitzgerald JR et al. Evolutionary genomics of *Staphylococcus aureus*: insights into the origin of methicillin-resistant strains and the toxic shock syndrome epidemic. *Proc Natl Acad Sci USA* 2001;98:8821-8826.
7. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997-1999. *MMWR* 1999;48(32):707-710.
8. Whitney CG et al. Increasing prevalence of multidrug resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000;343(26):1917-1924.
9. WHO Division of Control of Tropical Diseases. *Malaria control—burden and trends*.
10. WHO. *Global strategy for containment of antimicrobial resistance*.
11. CDC NNNIS semiannual report, June 2000.
12. WHO. *Food safety program*.
13. Cooper RA et al. Alternative mutations at position 76 of the vacuolar transmembrane protein PfCRT are associated with chloroquine resistance and unique stereospecific quinine and quinidine responses in *Plasmodium falciparum. Mol Pharmacol* 2002;61(1):35-42.
14. Matricardi PM et al. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol* 2002;110:381-387.
15. Beasley R et al. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;351:1225-1232.
16. Linneberg A et al. The prevalence of skin-test-positive allergic rhinitis in Danish adults: two cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. *Allergy* 2000;55:767-772.
17. CDC. Series 10, No. 205. Table 4. Percents (with standard errors) of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 1997. *www.cdc.gov/nchs/fastats/pdf/sr10_205t4.pdf*.
18. Beasley R et al., 1998.
19. *Ibid*.
20. Middleton E et al., eds. *Allergy: principles and practice*, fifth edition. St. Louis: Mosby, 1998, p. 1123.
21. Sampson HA. Peanut allergy. *N Engl J Med* 2002;346:1294-1299.
22. Sicherer SH. Food allergy. *Lancet* 2002;360:701-710.
23. Sicherer SH et al. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-562.
24. AAAAI. Anaphylaxis in schools and other child-care settings. Position statement #34. *J Allergy Clin Immunol* 1998;102:173-176.
25. Sampson HA et al. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327(6):380-384.
26. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994;69:16-23.
27. CDC. *MMWR* 2002;51:SS-1.

28. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001;107(1):3-8.

29. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. *Pediatrics* 2002;110(2):315-322.

30. CDC. *MMWR* 2002;51:SS-1.

31. Frey SE et al. for the National Institute of Allergy and Infectious Diseases Smallpox Vaccine Study Group. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002;346:1265-1274.

32. Shchelkunov SN et al. Analysis of the monkeypox virus genome. *Virology* 2002;297(2):172-194.

33. Hinnebusch BJ et al. Role of Yersinia murine toxin in survival of *Yersinia pestis* in the midgut of the flea vector. *Science* 2002;296(5568):733-735.

34. Pletnev AG et al. Tick-borne Langat/mosquito-borne dengue flavivirus chimera, a candidate live attenuated vaccine for protection against disease caused by members of the tick-borne encephalitis virus complex: evaluation in rhesus monkeys and in mosquitoes. *J Virol* 2001;75(17):8259-8267.

35. Pletnev AG et al. West Nile virus/dengue type 4 chimeras that reduced in neurovirulence and peripheral virulence without loss of immunogenicity or protective efficacy. *Proc Natl Acad Sci USA* 2002;99:3036-3041.

36. Dye C et al. Global burden of tuberculosis. *JAMA* 1999;282:677-686.

37. WHO. *Fact sheet* 104, August 2002. *www.who.int/mediacentre/factsheets/who104/en/index.html.*

38. WHO. *Global tuberculosis control*. WHO report 2001. *www.who.int/gtb/publications/globrep01*.

39. *MMWR* 2002;51(43):977-986. *www.cdc.gov/mmwr/preview/mmwrhtml/mm5143md.htm.*

40. Burgdorfer W et al. Lyme disease—a tick-borne spirochetosis? *Science* 1982;216:1317-1319.

41. Marques AR et al. Evaluation of the C6 peptide enzyme-linked immunosorbent assay for individuals vaccinated with the recombinant OspA vaccine. *J Clin Microbiol* 2002;40:2591-2593.

42. Hoyert DL et al. Deaths: final data for 1997. *Nat Vital Stat Rep* 1999;47(19):1-104.

43. Japanese authorities find third case of mad-cow disease. *Associated Press*. Tokyo, November 30, 2001. 19.

44. Priola SA et al. Porphyrin and phthalocyanine antiscrapie compounds. *Science* 2000;287: 1503-1506.

45. Caughey B, P.I. *Biochemistry of scrapie pathogenesis*. Annual Report No. 1 Z01 AI000580-12-LPVD.

46. WHO. *HCV fact sheet*, October 2000.

47. Kinzie JL et al. African Americans with genotype 1 treated with interferon for chronic hepatitis C have a lower end of treatment response than Caucasians. *J Viral Hepat* 2001;8(4):264-269.

48. *World health report* 2001.

49. Mu J et al. Chromosome-wide SNPs reveal an ancient origin for *Plasmodium falciparum*. *Nature* 2002;418:323-326.

50. Desai SA et al. A voltage-dependent channel involved in nutrient uptake by red blood cells infected with the malaria parasite. *Nature* 2000;406:1001-1005.

51. NHANES III. *The third national health and nutrition examination survey*.

52. CDC. *Reported tuberculosis in the United States*, 2000.

53. CDC. *Tracking the hidden epidemics: trends in STDs in the United States*, 2000. *www.cdc.gov/nchstp/dstd/stats_trends/trends2000.pdf.*

54. CDC. *AIDS surveillance reports*, December 31, 2001, Table 18.

55. Minkoff H et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. *AIDS* 2001;15:2157-2164.

56. Gange SJ. Effectiveness of highly active antiretroviral therapy among HIV-1 infected women. *J Epid Comm Health* 2002;56(2):153-159.

57. Robinson WR et al. Isotretinoin for low-grade cervical dysplasia in human immunodeficiency virus-infected women. *Obstet Gynecol* 2002;99(5):777-784.

58. CDC. *Tracking the hidden epidemics: trends in STDs in the United States*, 2000. *www.cdc.gov/nchstp/dstd/stats_trends/trends2000.pdf*.

59. *Ibid*.

60. United Network for Organ Sharing. *Critical data*. *www.unos.org*. Accessed October 3, 2002.

61. *Ibid*.

62. *Ibid*.

63. *Ibid*.

64. Scientific Registry of Transplant Recipients. *Fast facts*. *www.ustransplant.org*. Accessed October 4, 2002.

65. WHO. *Tuberculosis fact sheet* (1995-2005).

66. Rose NF et al. An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. *Cell* 2001;106(5):539-549.

67. Barouch D et al. Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature* 2002;145:335-339.

68. Schmidt AC et al. Mucosal immunization of rhesus monkeys against respiratory syncytial virus subgroups A and B and human parainfluenza virus type 3 by using a live cDNA-derived vaccine based on a host range-attenuated bovine parainfluenza virus type 3 vector backbone. *J Virol* 2002;76(3):1089-1099.

69. Emerson SU et al. Identification of VP1/2A and 2C as virulence genes of hepatitis A and demonstration of genetic instability of 2C. *J Virol* 2002;76(17): 8551-8859.

70. Baruch DI et al. Immunization of Aotus monkeys with a functional domain of the *Plasmodium falciparum* variant antigen induces protection against a lethal parasite line. *Proc Natl Acad Sci USA* 2002;99(6):3860-3865.

71. Hanley KA et al. Paired charge-to-alanine mutagenesis of dengue virus type 4 NS5 generates mutants with temperature-sensitive, host range, and mouse attenuation phenotypes. *J Virol* 2002;76(2):525-531.

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

The National Advisory Allergy and Infectious Diseases Council is composed of both scientists and laypersons. The Council makes final recommendations on the scientific merit of NIAID-assigned applications for research grants, cooperative agreements, and awards for research training activities. Review by the Council is the final step in the NIH peer review process. Council recommendations are based both on scientific merit, as judged by the scientific review groups, and on the relevance of the proposed study to the Institute's programs and priorities. Applications reviewed relate to all activities within the NIAID research mission, including the fields of immunology, allergic and immunologic diseases, transplantation immunology, microbiology and infectious diseases, and AIDS and AIDS-related conditions. Through its subcommittees, the Council conducts concept clearances and advises NIAID on general policy.

The National Advisory Allergy and Infectious Diseases Council roster is located at the Web site *www.niaid.nih.gov/facts/council.htm.*

Roster

Anthony S. Fauci, M.D. (Chair)
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

William E. Bertrand, Ph.D.
Executive Director
Payson Center for International Development and Technology Transfer
Tulane University
New Orleans, Louisiana 70118
(Term expires October 31, 2004)

Kim H. Bottomly, Ph.D.
Professor
Department of Immunobiology
School of Medicine
Yale University
New Haven, Connecticut 06520
(Term expires October 31, 2002)

Charlotte W. Collins, J.D.
Attorney
Powell, Goldstein, Frazier and Murphy
Washington, D.C. 2004
(Term expires October 31, 2004)

Luis A. Diaz, M.D.
Professor and Chairman
Department of Dermatology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599
(Term expires October 31, 2005)

Raif S. Geha, M.D.
Prince Turki Bin Abdul Aziz Al-Saud
Professor of Pediatrics
Department of Pediatrics
Harvard Medical School
Boston, Massachusetts 02115
(Term expires October 31, 2002)

Ellen H. Goldberg, Ph.D.
President
Santa Fe Institute
Santa Fe, New Mexico 87501
(Term expires October 31, 2002)

Barton F. Haynes, M.D.
Frederic M. Hanes Professor and Chair
Department of Medicine
School of Medicine
Duke University
Durham, North Carolina 22710
(Term expires October 31, 2002)

Jay B. Jackson, M.D.
Professor and Chairman of Pathology
Department of Pathology
Johns Hopkins Medical Institutions
Baltimore, Maryland 21287
(Term expires October 31, 2003)

William R. Jacobs, Jr., M.D.
Investigator
Howard Hughes Medical Institute
Albert Einstein College of Medicine
Bronx, New York 10461
(Term expires October 31, 2003)

Fred Jones, Jr., Ph.D.
Dean Emeritus
School of Graduate Studies and Research
Meharry Medical College
Nashville, Tennessee 37208
(Term expires October 31, 2004)

Dorothy E. Lewis, Ph.D.
Professor
Department of Immunology
Baylor College of Medicine
Houston, Texas 77030
(Term expires October 31, 2005)

Margaret A. Liu, M.D.
Vice Chairman, Transgene, S.A.
Visiting Professor
Karolinska Institute
Solna, Sweden
3656 Happy Valley Road
Lafayette, California 94549
(Term expires October 31, 2005)

Richard M. Locksley, M.D.
Chief
Division of Infectious Diseases
Department of Medicine
University of California, San Francisco
San Francisco, California 94143
(Term expires October 31, 2005)

Gerald L. Mandell, M.D.
Professor of Medicine
Owen R. Cheatham Professor of the Sciences
Chief, Division of Infectious Diseases
Department of Medicine
School of Medicine
University of Virginia Health Sciences Center
Charlottesville, Virginia 22908
(Term expires October 31, 2004)

John C. Martin, Ph.D.
President and Chief Executive Officer
Gilead Sciences, Incorporated
Foster City, California 94404
(Term expires October 31, 2003)

Marie M. Saint Cyr
Executive Director
Iris House, Incorporated
New York, New York 10030
(Term expires October 31, 2002)

Magdalene Y.H. So, Ph.D.
Chair
Department of Molecular Microbiology
and Immunology
School of Medicine
Oregon Health Sciences University
Portland, Oregon 97201
(Term expires October 31, 2003)

Thelma K. Thiel, R.N.
Chairperson and Chief Executive Officer
Hepatitis Foundation International
Cedar Grove, New Jersey 07009
(Term expires October 31, 2003)

EX OFFICIO MEMBERS

Lawrence R. Deyton, M.D.
Director, AIDS Service
U.S. Department of Veterans Affairs
Washington, D.C. 20420

James M. Hughes, M.D.
Director
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Department of Health and Human Services
Atlanta, Georgia 30333

Tommy G. Thompson
Secretary
Department of Health and Human Services
Washington, D.C. 20201

EXECUTIVE SECRETARY

John J. McGowan, Ph.D.
Director
Division of Extramural Activities
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

ACQUIRED IMMUNODEFICIENCY SYNDROME RESEARCH REVIEW COMMITTEE

In its role within the NIH peer review system, the Acquired Immunodeficiency Syndrome (AIDS) Research Review Committee advises the Directors of the NIH and NIAID with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The Committee provides a primary review of selected grant applications, cooperative agreements, and contract proposals for special research and training programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in AIDS-related areas. The Committee recommends ratings for those applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in the above-mentioned scientific areas.

The AIDS Research Review Committee roster is located at the Web site *www.niaid.nih.gov/facts/revcom.htm.*

Roster

Richard B. Markham, M.D. (Chair)
Professor
Department of Molecular Microbiology
and Immunology
Johns Hopkins School of Hygiene
and Public Health
Baltimore, Maryland 21205
(Term expires June 30, 2003)

Arlene D. Bardeguez, M.D.
Associate Professor
Department of Obstetrics and Gynecology
University of Medicine and Dentistry
New Jersey Medical School
Newark, New Jersey 07103
(Term expires June 30, 2004)

Yvonne J. Bryson, M.D.
Professor and Chief
Division of Infectious Diseases
School of Medicine
University of California, Los Angeles
Los Angeles, California 90095
(Term expires June 30, 2005)

Farley R. Cleghorn
Assistant Professor
Department of Medicine and Epidemiology
Institute of Human Virology
University of Maryland
Baltimore, Maryland 21201
(Term expires June 30, 2005)

Stephen Dewhurst, Ph.D.
Professor
Department of Microbiology and Immunology
School of Medicine and Dentistry
University of Rochester
Rochester, New York 14642
(Term expires June 30, 2003)

Robert W. Doms, M.D., Ph.D.
Chair
Department of Microbiology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104
(Term expires June 30, 2005)

Diane V. Havlir, M.D.
Associate Professor of Medicine
San Francisco General Hospital
San Francisco, California 94110
(Term expires June 30, 2004)

James E. Hildreth, M.D., Ph.D.
Professor
Department of Pharmacology
and Molecular Sciences
School of Medicine
Johns Hopkins University
Baltimore, Maryland 21205
(Term expires June 30, 2003)

Daniel R. Kuritzkes, M.D.
Director of AIDS Research
Partners AIDS Research Center
Cambridge, Massachusetts 02139
(Term expires June 30, 2005)

Marta L. Marthas, Ph.D.
Associate Adjunct Professor
California National Primate Research Center
School of Veterinary Medicine
University of California, Davis
Davis, California 95616
(Term expires June 30, 2005)

Nelson L. Michael, M.D., Ph.D.
Associate Professor
Division of Retrovirology
Department of Molecular Diagnostics
and Pathogenesis
Walter Reed Army Institute of Research
Rockville, Maryland 20850
(Term expires June 30, 2003)

James D. Neaton, Ph.D.
Professor
Division of Biostatistics
School of Public Health
University of Minnesota
Minneapolis, Minnesota 55414
(Term expires June 30, 2004)

Alagarsamy Srinivasan, Ph.D.
Professor
Department of Microbiology and Immunology
Thomas Jefferson University
Philadelphia, Pennsylvania 19107
(Term expires June 30, 2005)

Wayne A. Tompkins, Ph.D.
Director of Graduate Programs
North Carolina State University
College of Veterinary Medicine
Raleigh, North Carolina 27606
(Term expires June 30, 2004)

Scott W. Wong, Ph.D.
Associate Scientist
Division of Pathobiology and Immunology
Oregon Regional Primate Research Center
Beaverton, Oregon 97006
(Term expires June 30, 2002)

SCIENTIFIC REVIEW ADMINISTRATOR

Roberta Binder, Ph.D.
Scientific Review Administrator
Division of Extramural Activities
Acquired Immunodeficiency Syndrome
Research Review Committee
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

AIDS RESEARCH ADVISORY COMMITTEE

The AIDS Research Advisory Committee is mandated by Public Law 100-607, the Health Omnibus Programs Extension of 1988 (HOPE legislation), which was signed into law on November 4, 1988. The Committee advises and makes recommendations to the Director, NIAID, and to the Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), in all areas of biomedical research on HIV infection and AIDS related to the mission of DAIDS, including pathogenesis, natural history, and transmission of HIV disease, and to those efforts that support progress in its detection, treatment, and prevention.

The Committee provides broad scientific, programmatic, and budgetary advice on all aspects of HIV-related research supported by NIAID, including fundamental basic and clinical research, discovery and development of vaccines and other preventive interventions, and training of researchers in these activities. This activity includes the review of progress and productivity of ongoing efforts, assistance in identifying critical gaps/obstacles to progress, and approval of concepts for new initiatives.

The AIDS Research Advisory Committee roster is located online at *www.niaid.nih.gov/facts/arac.htm.*

Roster

King Holmes, M.D., Ph.D. (Chair)
Director, Center for AIDS and STDs
University of Washington
Seattle, Washington 98104
(Term expires June 30, 2005)

Moises Agosto
Vice President of Program Development
Community Access
New York, New York 10016
(Term expires June 30, 2005)

Henry H. Balfour, Jr., M.D.
Professor
Department of Microbiology and Pathology
University of Minnesota
Minneapolis, Minnesota 55455
(Term expires June 30, 2004)

Robert E. Johnston, Ph.D.
Professor
Department of Microbiology and Immunology
University of North Carolina
Chapel Hill, North Carolina 27599
(Term expires June 30, 2004)

Phyllis J. Kanki, D.V.M., S.D.
Professor of Immunology and Infectious Disease
Harvard School of Public Health
Boston, Massachusetts 02115
(Term expires June 30, 2006)

Preston A. Marx, Ph.D.
Tulane Regional Primate Research Center
Covington, Louisiana 70433
(Term expires June 30, 2004)

Andrea Jenay Ruff, M.D.
Associate Professor of International Health
Johns Hopkins University School of Hygiene and Public Health
Baltimore, Maryland 21287-4933
(Term expires June 30, 2005)

EX OFFICIO MEMBERS

Harold W. Jaffe, M.D.
Acting Director
National Center for HIV, STD,
and TB Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

Henry Masur, M.D.
Chief, Critical Care Medicine
National Institutes of Health Clinical Center
Bethesda, Maryland 20892

Jack Whitescarver, Ph.D.
Director
Office of AIDS Research
National Institutes of Health
Bethesda, Maryland 20892

OFFICE OF AIDS RESEARCH ADVISORY COUNCIL LIAISON

Robert E. Booth, Ph.D.
Professor, Department of Psychiatry Addiction Research and Treatment
University of Colorado Health Sciences Center
School of Medicine
Denver, Colorado 80262

EXECUTIVE SECRETARY

Rona Siskind
Executive Secretary
AIDS Research Advisory Committee
Division of AIDS
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

AIDS VACCINE RESEARCH WORKING GROUP

The AIDS Vaccine Research Working Group, established in February 1997, assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine. The individuals in this group provide advice regarding the vaccine research programs at the NIH with respect to scientific opportunities, gaps in knowledge, and future directions of research. The Working Group, which reports to the NIAID Council, is chaired by Dr. Barton Haynes and is composed of individuals with expertise in immunology, structural biology, virology, animal models, and vaccine development.

The AIDS Vaccine Research Working Group roster is located at the Web site *www.niaid.nih.gov/aidsvaccine/avrc.htm.*

Roster

Barton F. Haynes, M.D. *(Chair)*
Frederic M. Hanes Professor, and Chair
Department of Medicine
School of Medicine
Duke University
Durham, North Carolina 27710

Raphael Dolin, M.D.
Dean for Clinical Programs
Harvard Medical School
Boston, Massachusetts 02115

R. Gordon Douglas, Jr., M.D.
Consultant
Vaccines, Infectious Diseases, and Global Health
Princeton, New Jersey 08540

Beatrice H. Hahn, M.D.
Professor
University of Alabama at Birmingham
Birmingham, Alabama 35294-0007

Stephen C. Harrison, Ph.D.
Investigator, Howard Hughes Medical Institute
Professor of Biochemistry
Harvard University
Cambridge, Massachusetts 02138

Dennis Kasper, M.D.
Professor, Department of Medicine, Microbiology, and Molecular Genetics
Harvard Medical School
Boston, Massachusetts 02115-6902

Bette Korber, Ph.D.
Los Alamos National Laboratory
Los Alamos, New Mexico 87545

Norman Letvin, M.D.
Professor of Medicine
Harvard Medical School
Chief, Division of Viral Pathogenesis
Beth Israel Deaconess Medical Center
Boston, Massachusetts 02215

John P. Moore, Ph.D.
Professor of Microbiology and Immunology
Joan and Sanford I. Weill Medical College of Cornell University
New York, New York 10021

Neal Nathanson, M.D.
Vice Provost for Research
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania 19104-6303

Douglas Richman, M.D.
Professor
University of California at San Diego
La Jolla, California 92093

William Snow
AIDS Vaccine Advocacy Coalition
Berkeley, California 94708

ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION RESEARCH COMMITTEE

The Allergy, Immunology, and Transplantation Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of allergy, clinical immunology, immunopathology, immunobiology, immunogenetics, immunochemistry, and transplantation biology. The Committee provides primary review of grant applications and special research programs. These include program projects, institutional National Research Service Awards, conference grants, and special developmental award programs. The Committee recommends ratings for those applications that it determines to have significant and substantial scientific merit.

The Allergy, Immunology, and Transplantation Research Committee roster is located at the Web site *www.niaid.nih.gov/facts/revcom.htm#CVH16.*

Roster

Paula B. Kavathas, Ph.D. (Chair)
Professor
Departments of Laboratory Medicine
and Genetics, School of Medicine
Yale University
New Haven, Connecticut 06520
(Term expires June 30, 2003)

Rafeul Alam, M.D., Ph.D.
Professor and Director
Veda and Chauncey Ritter Chair
in Immunology
National Jewish Medical and Research Center
Division of Allergy and Immunology
Denver, Colorado 80206
(Term expires June 30, 2004)

Charles L. Bevins, M.D., Ph.D.
Associate Member
Department of Immunology
Lerner Research Institute
The Cleveland Clinic Foundation
Cleveland, Ohio 44195
(Term expires June 30, 2002)

William J. Burlingham, Ph.D.
Associate Professor
Department of Surgery
University of Wisconsin Medical School
Madison, Wisconsin 53792
(Term expires June 30, 2005)

Anita S. Chong, Ph.D.
Associate Professor
University of Chicago
Department of Surgery
Chicago, Illinois 60637
(Term expires June 30, 2003)

Daniel H. Conrad, Ph.D.
Professor
Department of Microbiology and Immunology
Virginia Commonwealth University
Richmond, Virginia 23928
(Term expires June 30, 2004)

Jeffrey A. Frelinger, Ph.D.
Professor
Department of Microbiology and Immunology
University of North Carolina
Chapel Hill, North Carolina 27599
(Term expires June 30, 2003)

Kathryn Haskins, Ph.D.
Professor
823 Goodman Building
Department of Immunology
University of Colorado Health Sciences Center
Denver, Colorado 80106
(Term expires June 30, 2005)

David P. Huston, M.D.
Cullen Chair in Immunology
Departments of Medicine, Microbiology, and Immunology
Baylor College of Medicine
Houston, Texas 77030
(Term expires June 30, 2003)

Fadi G. Lakkis, M.D.
Associate Professor
Section of Nephrology
Department of Medicine
Yale University School of Medicine
New Haven, Connecticut 06520
(Term expires June 30, 2003)

Shoshana Levy, Ph.D.
Professor
Department of Medicine/Oncology
School of Medicine
Stanford University
Stanford, California 94305
(Term expires June 30, 2005)

Nicholas W. Lukacs, Ph.D.
Associate Professor
Department of Pathology
School of Medicine
University of Michigan
Ann Arbor, Michigan 48109
(Term expires June 30, 2005)

Larry W. Moreland, M.D.
Associate Professor of Medicine
Department of Medicine
School of Medicine
University of Alabama at Birmingham
Birmingham, Alabama 35294
(Term expires June 30, 2002)

Daniel L. Mueller, M.D.
Associate Professor
Center for Immunology
University of Minnesota
Minneapolis, Minnesota 55455
(Term expires June 30, 2002)

Andre E. Nel, M.D., Ph.D.
Professor of Medicine
Department of Medicine
School of Medicine
University of California, Los Angeles
Los Angeles, California 90095
(Term expires June 30, 2004)

Shiguang Qian, M.D.
Associate Professor
Department of Surgery
Thomas E. Starzi Transplantation Institute
University of Pittsburgh Medical School
Pittsburgh, Pennsylvania 15213
(Term expires June 30, 2005)

Alkis G. Togias, M.D.
Associate Professor of Medicine
Divisions of Clinical Immunology and Pulmonary and Critical Care Medicine
Johns Hopkins Asthma and Allergy Center
Johns Hopkins University
Baltimore, Maryland 21224
(Term expires June 30, 2003)

Anne M. VanBuskirk, Ph.D.
Assistant Professor
Department of Surgery
College of Medicine
Ohio State University
Columbus, Ohio 43210
(Term expires June 30, 2004)

SCIENTIFIC REVIEW ADMINISTRATOR AND EXECUTIVE SECRETARY

Nancy B. Saunders, Ph.D.
Scientific Review Administrator
Science Review Program
Division of Extramural Activities
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892
(Term expires June 30, 2007)

MICROBIOLOGY AND INFECTIOUS DISEASES RESEARCH COMMITTEE

The Microbiology and Infectious Diseases Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in microbiology and infectious diseases. Specialized areas of concern include molecular biology, microbial chemistry, parasitology, virology, bacteriology, mycology, vaccine development, and antimicrobial chemotherapy. The Committee provides a primary review of grant applications, cooperative agreements, and contract proposals for special research programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in the areas mentioned above. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in these scientific areas.

The Microbiology and Infectious Diseases Research Committee roster is located online at *www.niaid.nih.gov/facts/revcom.htm#SAL32*.

Roster

Sheila A. Lukehart, Ph.D. (Chair)
Professor
Department of Medicine and
Infectious Diseases
School of Medicine
University of Washington
Harborview Medical Center
Seattle, Washington 98195
(Term expires June 30, 2002)

Michael J. Buchmeier, Ph.D.
Professor
Department of Neuropharmacology
The Scripps Research Institute
La Jolla, California 92037
(Term expires June 30, 2005)

Arturo Casadevall, M.D., Ph.D.
Professor
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York 10461
(Term expires June 30, 2005)

Henry F. Chambers, M.D.
Professor
Department of Medicine
School of Medicine
University of California, San Francisco
San Francisco, California 94143
(Term expires June 30, 2002)

John Hay, Ph.D.
Grant T. Fisher Chair and Professor
Department of Microbiology
School of Medicine and Biomedical Sciences
State University of New York at Buffalo
Buffalo, New York 14214
(Term expires June 30, 2002)

Randall K. Holmes, M.D., Ph.D.
Professor and Chair
Department of Microbiology
University of Colorado Health Sciences Center
Denver, Colorado 80262
(Term expires June 30, 2004)

Clifford W. Houston, Ph.D.
Professor
Department of Microbiology and Immunology
School of Medicine
University of Texas Medical Branch
Galveston, Texas 77555
(Term expires June 30, 2003)

Karla A. Kirkegaard, Ph.D.
Professor
Department of Microbiology and Immunology
School of Medicine
Stanford University
Stanford, California 94395
(Term expires June 30, 2002)

Jean C. Lee, Ph.D.
Associate Professor
Department of Medicine
Channing Laboratory
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts 02115
(Term expires June 30, 2003)

Anna Suk-Fong Lok, M.D.
Professor
Division of Gastroenterology
Department of Internal Medicine
University of Michigan Medical Center
Ann Arbor, Michigan 48109
(Term expires June 30, 2002)

Diane M. McMahon-Pratt, Ph.D.
Professor
Department of Epidemiology and Public Health
Yale University School of Medicine
New Haven, Connecticut 06510
(Term expires June 30, 2004)

Thomas G. Mitchell, Ph.D.
Associate Professor
Department of Microbiology
School of Medicine
Duke University Medical Center
Durham, North Carolina 27710
(Term expires June 30, 2003)

William A. Petri, Jr., M.D., Ph.D.
Professor
Department of Medicine
and Infectious Diseases
University of Virginia Health System
Charlottesville, Virginia 22908
(Term expires June 30, 2005)

John J. Treanor, M.D.
Professor
Department of Infectious Diseases Unit
University of Rochester School of Medicine
Rochester, New York 14642
(Term expires June 30, 2004)

Christopher C. Whalen, M.D.
Associate Professor
Department of Epidemiology and Biostatistics
School of Medicine
Case Western Reserve University
Cleveland, Ohio 44106
(Term expires June 30, 2003)

SCIENTIFIC REVIEW ADMINISTRATOR

Gary Madonna, Ph.D.
Microbiology and Infectious Diseases
Research Committee
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

BOARD OF SCIENTIFIC COUNSELORS

The Board of Scientific Counselors advises the Director, NIH, the Deputy Director for Intramural Research, NIH, the Director, NIAID, and the Director, Division of Intramural Research (DIR), NIAID, concerning the Institute's intramural research programs. The Board's recommendations are based on rigid and objective reviews of NIAID laboratories to assess ongoing research, as well as future directions, and to evaluate the productivity and performance of NIAID's tenured scientists, tenure-track scientists, and the Scientific Director. Following each review, the written report from the Board is forwarded, with a response from the Director, DIR, NIAID, to the Deputy Director for Intramural Research, NIH. In addition, the Board's recommendations are communicated annually to the National Advisory Allergy and Infectious Diseases Council.

The Board's review process strengthens NIAID's tenure system and the overall quality of the Institute's research. As a result of the Board's scientific review, NIAID may modify or redirect its intramural research priorities to allow for scientific growth of investigators as well as pursuit of important new areas of research. Its findings have a direct impact on the allocation of personnel, budget, and space resources within each laboratory.

The Board of Scientific Counselors roster is located at the Web site *www.niaid.nih.gov/facts/bscroste.htm.*

Roster

Donald J. Capra, M.D. (Chair)
President and Scientific Director
Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma 73104
(Term expires June 30, 2002)

Frances M. Brodsky, D.P.H.L.
Professor
Department of Biopharmaceutical Sciences
The G.W. Hooper Foundation
University of California at San Francisco
San Francisco, California 94143-0552
(Term expires June 30, 2004)

Irma Gigli, M.D.
Professor of Medicine
Institute of Molecular Medicine for the Prevention of Human Diseases
University of Texas Houston Health Science Center
Houston, Texas 77030
(Term expires June 30, 2002)

George V. Hillyer III, Ph.D.
Professor and Director
Rio Piedras Campus
University of Puerto Rico
San Juan, Puerto Rico 00931-3300
(Term expires June 30, 2004)

Elliott D. Kieff, M.D., Ph.D.
Professor
Infectious Diseases Division
Department of Microbiology and Molecular Genetics
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts 02115
(Term expires June 30, 2003)

Robert S. Munford, M.D.
Jan and Henri Bromberg Chair in Internal Medicine
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas 75390-9113
(Term expires June 30, 2004)

Barbara A. Osborne, Ph.D.
Professor
Department of Veterinary and Animal Sciences
University of Massachusetts
Amherst, Massachusetts 01003
(Term expires June 30, 2002)

Richard J. Whitley, M.D.
Professor of Pediatrics
Department of Pediatrics
Children's Hospital
University of Alabama at Birmingham
Birmingham, Alabama 35233
(Term expires June 30, 2004)

EXECUTIVE SECRETARY

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

NIAID EXECUTIVE COMMITTEE

The Executive Committee is the senior internal policy and advisory group to the Director, NIAID, and acts as a forum for discussing and setting important Institute-wide scientific and management policies and for discussing special issues and concerns that affect NIAID programs. As such, the Executive Committee consists of NIAID senior scientific and management staff, as well as several ad hoc members who provide program-staff-level input. All new, expansion, and renewal program initiatives are reviewed by the Executive Committee at the earliest possible stage of project development to provide the NIAID Director and senior staff the opportunity to discuss and consider the merit and relationship of all projects to the ongoing programs of the Institute. The Executive Committee also serves as the vehicle for senior NIAID management to communicate with Institute program staff regarding issues and policies that are being considered for implementation at both the NIAID and NIH levels.

The Executive Committee roster is located at the Web site *www.niaid.nih.gov/facts/executivecom.htm.*

Roster

Anthony S. Fauci, M.D. (Chair)
Director

John R. La Montagne, Ph.D.
Deputy Director

Lynn C. Hellinger
Associate Director for Management and Operations

Nancy Blustein
Director
Office of Policy Analysis

Laurie Doepel
Acting Director
Office of Communications and Public Liaison

Mark Dybul, M.D.
Assistant Director for Medical Affairs
Office of the Director

Gregory K. Folkers
Special Assistant for Research Reporting
Office of the Director

Richard Freed
Director
Office of Management for New Initiatives

Carole A. Heilman, Ph.D.
Director
Division of Microbiology and Infectious Diseases

Milton J. Hernandez, Ph.D.
Director
Office of Special Populations and Research Training

Elizabeth A. Holmes
Acting Director
Office of Human Resources Management

Jack Killen, M.D.
Assistant Director for Biodefense Research
Office of the Director

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research

H. Clifford Lane, M.D.
Director
Office of Clinical Research

John J. McGowan, Ph.D.
Director
Division of Extramural Activities

Michael Mowatt, Ph.D.
Director
Office of Technology Development

Gary Nabel, M.D., Ph.D.
Director
Vaccine Research Center

Roger E. Pellis
Executive Officer and Director
Office of Administrative Services

Daniel Rotrosen, M.D.
Director
Division of Allergy, Immunology and Transplantation

Karen Santoro, J.D.
Director
Office of Ethics

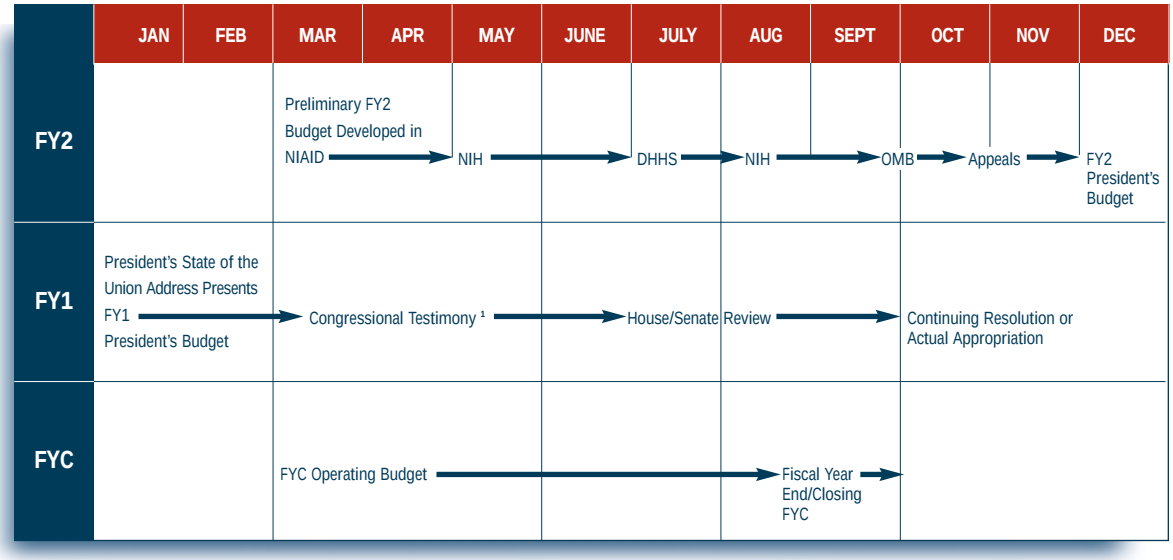
Ralph Tate
Director
Office of Financial Management

Ed Tramont, M.D.
Director
Division of Acquired Immunodeficiency Syndrome

Karl A. Western, M.D., D.T.P.H.
Assistant Director for International Research
Office of the Director

Laurence B. Wolfe, Ph.D.
Director
Office of Technology Information Systems

FEDERAL BUDGET PROCESS

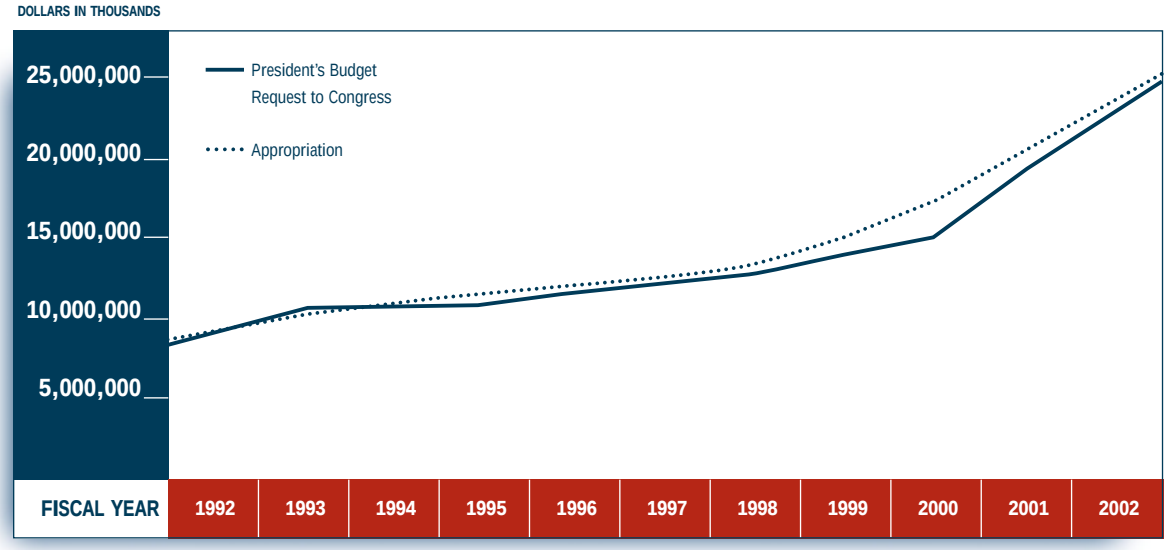


FISCAL YEAR = OCTOBER 1 TO SEPTEMBER 30

FY2 = SECOND FUTURE FISCAL YEAR
FY1 = FIRST FUTURE FISCAL YEAR
FYC = CURRENT FISCAL YEAR

1 NIH Director and NIH IC Directors, including Director, NIAID, provide congressional testimony to the House and Senate Appropriations Subcommittees on Labor, Health and Human Services, and Education.

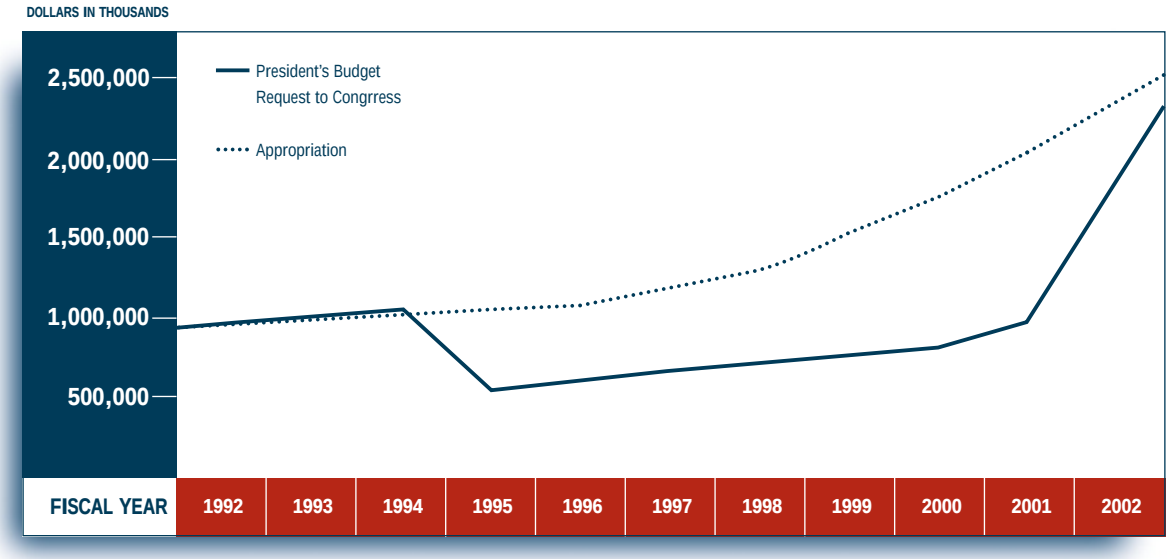
NIH APPROPRIATIONS HISTORY: FY 1992-2002



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation[a]
	(Dollars in Thousands)			
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 [b]
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 [c]
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,937,653,000 [d]
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,299,522,000 [e]
1996	11,773,066,000	11,939,001,000	11,639,204,000	11,927,562,000 [f]
1997	12,406,300,000 [g]	12,747,203,000	12,414,580,000 [h]	12,740,843,000 [i]
1998	13,078,203,000 [j]	13,505,294,000	13,692,844,000	13,647,843,000 [k]
1999	14,763,313,000 [l]	14,862,023,000	15,622,385,000	15,612,386,000 [m]
2000	15,932,786,000	16,936,314,000	17,613,470,000	17,826,571,000
2001	18,812,735,000	20,512,735,000	20,512,735,000	20,361,130,000
2002	23,041,902,000	22,874,971,000	23,695,260,000	23,175,843,000 [n]

a Reflects enacted supplementals, rescissions, and reappropriations.
b Reflects enacted administrative reduction of $69,608,000 for salaries and expenses, a travel reduction of $5,984,000, and a rescission of $13,131,000.
c Reflects enacted administrative reduction of an across-the-board 0.8 percent of $83,571,000, $34,857,000 for salaries and expenses, and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.
d Reflects a salaries and expense rescission of $18,120,000. Excludes $1,000,000 supplemental in NCRR for earthquake relief.
e Includes $1,299,328,000 for NIH research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of $7,446,000 for procurement, $345,000 for rent and $4,401,000 for bonus pay, and rescission of $10,000,000 in NCRR for construction and $12,384,000 in administrative costs.
f Includes $1,410,925,000 appropriated to the ICDs for HIV research. Incorporates the NIH share of the Government-wide administrative cost rescission ($5,780,000) and the Labor/HHS/Education bonus pay rescission ($5,659,000).
g Includes $1,431,908,000 for HIV research in the NIH Office of AIDS Research.
h Includes $1,460,312,000 for HIV research in the NIH Office of AIDS Research.
i Includes $$1,501,073,000 for HIV research in the NIH Office of AIDS Research. Incorporated the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000).
j Includes $1,540,765,000 for HIV research in the NIH Office of AIDS Research.
k Includes $1,607K053,000 appropriated to the ICs for HIV research.
l Reflects a decrease of $34,530,000 for the budget amendment of bioterrorism. Includes $1,728,099,000 for HIV research in the NIH Office of AIDS Research.
m Includes $1,798,424,000 appropriated to the ICs for HIV research.
n Includes $2,535,672,000 appropriated to the ICs for HIV research. Reflects NIH share of across-the-board reduction ($9,273,000) and transfer for $100M to the Global Fund for HIV/AIDS, malaria, and tuberculosis.

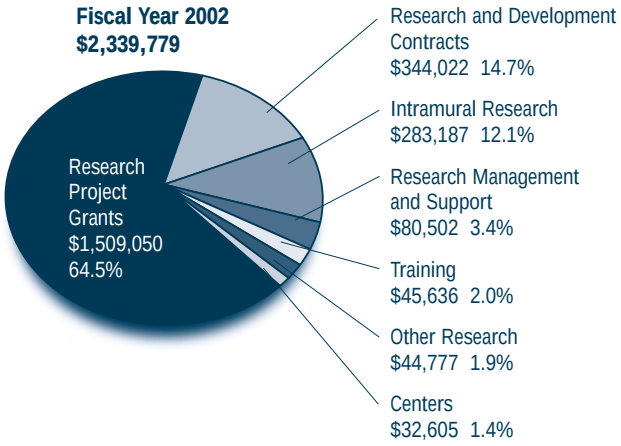
NIAID APPROPRIATIONS HISTORY: FY 1992—2002

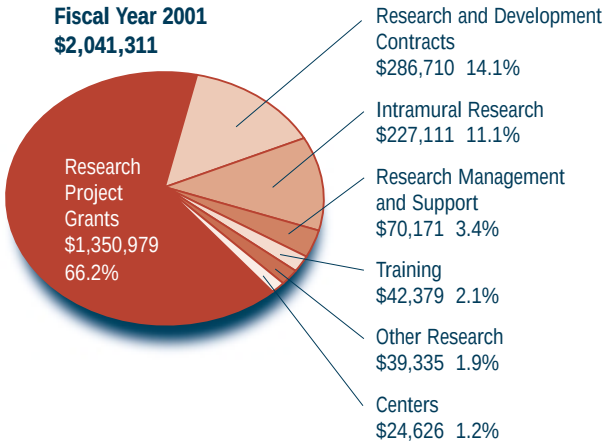


Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation[a]
	(Dollars in Thousands)			
1992	976,711	972,830	965,952	959,914 [b]
1993	1,010,845	990,055	989,055	979,471 [c]
1994	1,065,583	1,065,583	1,065,583	1,063,704 [d]
1995	542,864 [e]	1,094,633	1,094,633	1,092,507 [f]
1996	557,354 [e]	1,169,628	1,139,326	1,171,168 [g]
1997	584,362 [e]	1,256,149	1,229,009	1,257,794 [h]
1998	634,272 [e]	1,339,459	1,359,688	1,352,119 [i]
1999	703,723 [e,j]	1,470,460	1,540,102	1,569,063
2000	789,156	1,694,019	1,786,718	1,797,988 [k]
2001	936,166	2,062,126 [l]	2,066,526	2,069,388
2002	2,355,325	2,337,204	2,375,836	2,535,788

a Reflects enacted supplementals, rescissions, and reapporprations.
b Excludes an enacted administrative reduction of $11,197,000.
c Excludes an enacted administrative reduction of $12,334,000.
d Includes rescission of $1,879,000.
e Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
f Includes a rescission of $1,293,000 and a transfer of $458,000.
g Includes an enacted administrative reduction of $1,145,000 and a net NIH Director's transfer of $2,685.
h Includes a rescission of $575,000 for administrative expenses and a net positive transfer of $1,135,000 from the NIH Director's Reserve.
i Includes rescissions and transfers.
j Reflects an increase of $1,683,000 for the budget amendment for bioterrorism.
k Includes a rescission of $5,075,000.
l Represents program level.

NIAID FUNDING BY BUDGET MECHANISM: FY 2001–2002

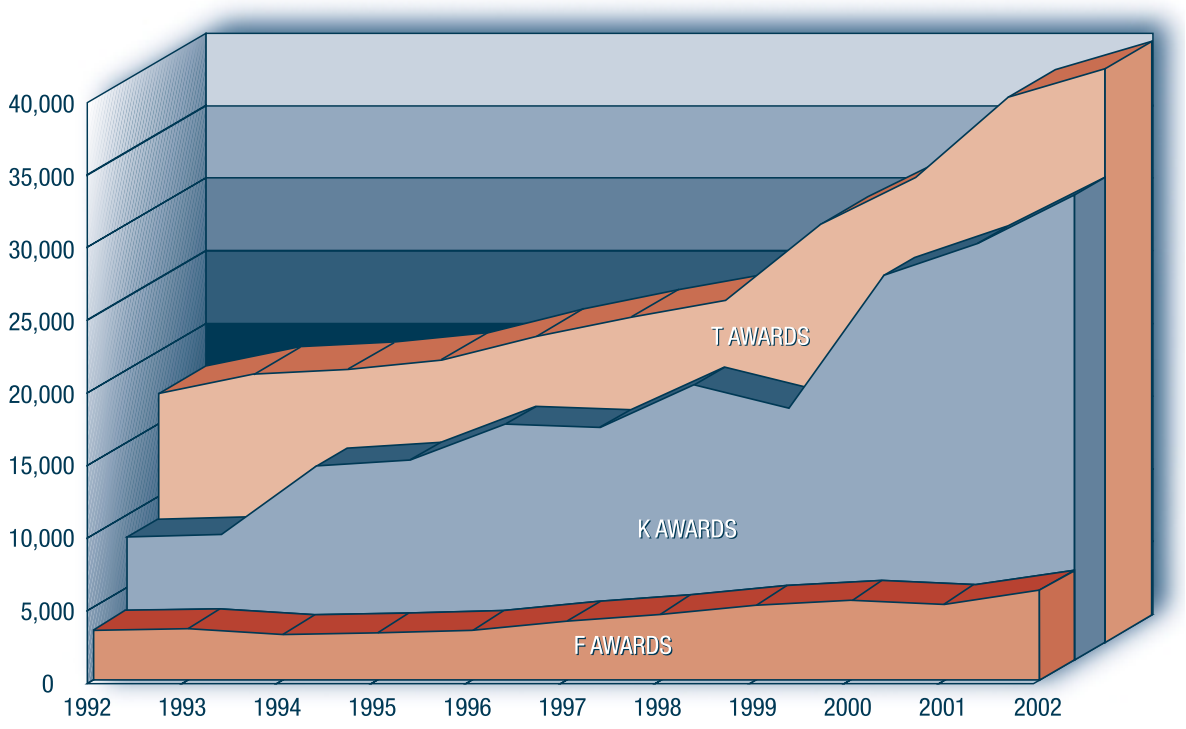




Budget Mechanism	FY 2002[a]	% of Total	FY 2001[a]	% of Total	% Change
Research Project Grants (RPG's)					
Noncompeting	$1,103,835		$990,590		
Competing	334,818		360,389		
Subtotal, RPGs	1,509,050	64.5	1,350,979	66.2	+11.7
Centers	32,605	1.4	24,626	1.2	+32.4
Other Research	44,777	1.9	39,335	1.9	+13.0
Training	45,636	2.0	42,379	2.1	+7.7
R&D Contracts	344,022	14.7	286,710	14.1	+20.0
Subtotal, Extramural	1,967,090		1,744,029		+12.8
Intramural Research	283,187	12.1	227,111	11.1	+24.7
Research Management and Support	80,502	3.4	70,171	3.4	+14.7
Total	**$2,339,779**		**$2,041,311**		**+14.6**

[a] Dollars in thousands and reflects "Actuals" versus appropriations.

NIAID RESEARCH TRAINING AND CAREER AWARDS[a]: FY 1992-2002 (DOLLARS IN THOUSANDS)



[a] Includes F31, F32, F33, F34, K04, K06, K07, K08, K11, T32, T35, and T36 awards (described in the NIH Extramural Funding Mechanisms appendix).

	T AWARDS (INSTITUTIONAL AWARDS)		K AWARDS (CAREER AWARDS)		F AWARDS (INDIVIDUAL TRAINING AWARDS)	
Fiscal Year	No. Awards	Dollar Amount	No. Awards	Dollar Amount	No. Awards	Dollar Amount
1992	114	$17,379	117	$8,689	127	$3,587
1993	116	18,550	117	8,818	128	3,606
1994	115	18,894	174	13,411	125	3,378
1995	118	19,539	176	13,884	124	3,386
1996	123	21,254	204	16,566	126	3,439
1997	140	22,478	204	16,159	150	4,067
1998	152	23,738	211	16,908	151	4,350
1999	148	29,092	205	17,686	146	5,177
2000	164	32,035	241	26,863	161	5,709
2001	923	37,113	245	28,885	146	5,266
2002	919	39,474	272	32,237	153	6,162

Appendices

LEGISLATIVE CHRONOLOGY

NOV. 1, 1948

The National Microbiological Institute was established under authority of section 202 of the Public Health Service Act, as implemented by General Circular No. 55, Organization Order No. 20, dated October 8, 1948.

DEC. 29, 1955

NIAID was established (replacing the National Microbiological Institute) under authority of the Omnibus Medical Research Act (Public Law 81-692, 64 Stat. L. 443), as implemented by a Public Health Service Briefing Memorandum of November 4, 1955, from the Surgeon General to the Secretary of Health, Education, and Welfare.

NOV. 4, 1988

NIAID was provided with additional authorities for AIDS research under Title II of the Health Omnibus Programs Extension of 1988 (HOPE legislation) (Public Law 100-607), the first major law to address AIDS research, information, education, and prevention.

AUG. 14, 1991

The Public Health Service Act was amended by Public Law 102-96, the Terry Beirn Community-Based AIDS Research Initiative Act of 1991, which reauthorized NIAID's Community Programs for Clinical Research on AIDS (CPCRA). CPCRA was renamed in honor of Mr. Beirn (an AIDS activist and congressional staffer who died in 1991) and was reauthorized for an additional 5 years.

JUNE 10, 1993

The Public Health Service Act was amended by Public Law 103-43, the National Institutes of Health Revitalization Act of 1993. This comprehensive legislation required NIAID to include research on tropical diseases in its mission statement and directs the Secretary, U.S. Department of Health and Human Services, to ensure that individuals with expertise in chronic fatigue syndrome or neuromuscular diseases are appointed to appropriate NIH advisory committees.

DEC. 14, 1993

The Preventive Health Amendments of 1993 were passed, which included provisions requiring the Director, NIAID, to conduct or support research and research training regarding the cause, early detection, prevention, and treatment of tuberculosis. (The Institute already had authority to conduct such research under its authorities in Title IV, Public Health Service Act.)

NOV. 29, 1999

The FY 2000 Appropriations Act (Public Law 106-113) established the NIH Challenge Grants program to promote joint ventures between the NIH and the biotechnology, pharmaceutical, and medical device industries. A one-time funding level of $20 million was provided within the Public Health and Social Services Emergency Fund.

OCT. 17, 2000

The Children's Health Act (Public Law 106-310) required the Directors of NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases to expand and intensify the activities of their Institutes with respect to research and related activities concerning juvenile arthritis and related conditions.

NOV. 13, 2000

The Public Health Improvement Act (Public Law 106-505) authorized the NIAID Director to establish a program of clinical research and training awards for sexually transmitted diseases.

Previous Directors

Victor H. Haas, M.D., 1948-1957
Justin M. Andrews, Sc.D., 1957-1964
Dorland J. Davis, M.D., D.P.H., 1964-1975
Richard M. Krause, M.D., 1975-1984

TECHNOLOGY TRANSFER

Technology transfer in Federal laboratories facilitates the dissemination of new technologies and research materials developed by Government scientists. This technology transfer fuels further innovation and commercialization by the extramural research and development community, ultimately resulting in an improvement in the public health and an increase in the competitiveness of U.S. industry. Federal legislation mandates and defines the Government's technology transfer activities. The key pieces of legislation are the Federal Technology Transfer Act of 1986 and the National Technology Transfer and Advancement Act of 1995.

The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and the development of collaborative relationships between NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Cooperative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADAs), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements (DSAs), and, through the NIH Office of Technology Transfer (OTT), the patenting of inventions and the negotiation of various license agreements.

NIAID scientists report inventions to OTD by submitting Employee Invention Reports (EIRs). The EIRs are reviewed by OTD and, with the assistance of the NIAID Technology Evaluation Advisory Committee (TEAC), are evaluated for the purpose of filing domestic and foreign patent applications. In FY 2002, TEAC reviewed 21 intramural EIRs and recommended that a patent application be filed on 16 of them. NIAID currently has 286 active U.S. patent properties, including 139 issued patents and 147 pending patent applications.

NIAID had a total of 197 active license agreements in FY 2002 for both patented inventions and biological materials. These licenses generated about $9.8 million in royalty income, which was first used to pay NIAID inventors their share according to Federal law and NIH policy. The Institute also distributed royalty income to intramural laboratories to support research projects and equipment acquisition that otherwise would not have been accomplished with appropriated funds. The remaining royalties were used to pay OTD's entire operating budget, including patent prosecution fees, OTD staff salaries, associated office expenses, and overhead charged by OTT.

In FY 2002, a total of 141 MTAs, 5 CTAs, 69 CDAs, 8 CRADAs, 19 M-CRADAs, and 16 other agreements were executed, which OTD negotiated. Extramural divisions referred technology transfer issues to OTD on 10 contracts. OTD NIAID scientists performed research under 36 CRADAs and 49 M-CRADAs in FY 2002. The following table provides a history of NIAID's patent, license, and CRADA activities.

NIAID Technology Transfer Activities

Fiscal Year	Pending Patents	Issued Patents	Licenses in Effect	Active CRADAs
1992	77	48	65	21
1994	85	65	84	29
1995	96	71	101	31
1996	95	84	120	42
1997	128	91	131	71
1998	154	83	155	95
1999	169	94	195	74
2000	229	100	196	86
2001	194	125	190	93
2002	147	139	197	85

Technology Transfer Highlights

In FY 2002, OTD negotiated or facilitated the following public-private partnerships.

AIDS DNA Vaccine (Vical)

Under this M-CRADA (Effect of Poloxamers on Immune Responses to HIV DNAs), investigators in the Viral Immunology Laboratory, Vaccine Research Center (VRC), NIAID, NIH, seek to evaluate materials that may enhance expression and/or improve immune responses to DNA vaccines.

Malaria Vaccine (Maxygen)

The parasite *Plasmodium falciparum* is a major cause of sickness and death in sub-Saharan Africa. The interactions between malaria-parasitized erythrocytes and host cells contribute to the pathogenesis of the disease, in particular the development of cerebral malaria. Antibodies to the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) block the adherence and sequestration functions of parasitized red blood cells; PfEMP1 therefore represents a clear vaccine candidate. Immunization with the CIDR1 domain of PfEMP1 elicits strong protective immunity in Aotus monkeys against an otherwise lethal challenge with the homologous parasite. However, the sequence and domain structure of PfEMP1 is highly variable among different parasite isolates. Under this CRADA, NIAID and Maxygen will use Maxygen's MolecularBreeding™ directed molecular evolution technologies to engineer a PfEMP1 immunogen that will protect against diverse parasite variants and thus provide protective immunity and decreased cerebral malaria pathology. These technologies can create chimeric protein variants displaying enhanced or novel activities. The application of this approach to the development of PfEMP1 antigens that encompass multiple reactivities as vaccines against numerous strains of *P. falciparum* represents a novel and powerful approach to solving one of the main barriers to malaria vaccine development.

Leishmaniasis Vaccine (Merial)

NIAID and Merial Limited are working together to make and evaluate the first vector-based candidate vaccine to combat canine leishmaniasis. Current efforts are focused on evaluating candidate DNA vaccines that express salivary gland proteins of the sand flies that carry the *Leishmania* pathogen, which causes the disease leishmaniasis, a severe parasitic disease in dogs. An effective veterinary vaccine will provide significant benefit to veterinary medicine and may pave the way for human vaccines against leishmaniasis. The vaccination of animals may also have a significant impact on the epidemiology of the disease by reducing the reservoirs of leishmaniasis.

Ebola Vaccine (Crucell)

Recombinant adenoviral vectors have been widely investigated in recent years as a gene

delivery system for gene therapy and vaccination. Recombinant adenoviral vectors offer a promising strategy for the development of a candidate Ebola vaccine that could be effective in humans. The NIH VRC and Crucell NV will collaborate to evaluate and develop adenoviral vectors expressing modified Ebola genes. The collaboration will evaluate such adenovectors for potential application as an Ebola preventative or therapeutic vaccine. The VRC will provide Crucell with several modified Ebola genes, and Crucell will construct and produce recombinant adenovectors that express Ebola genes utilizing the Crucell adenovector and PER.C6 cell line system. These adenoviral vectors will be evaluated *in vitro* and *in vivo* at the VRC.

New CRADAs

During FY 2002, NIAID scientists entered into the following eight new CRADAs:

Collaborator
Ciphergen Biosystems

Investigators
John Kehrl, M.D.
Tae-Wook Chun, Ph.D.
Laboratory of Immunoregulation

Title
Identification and characterization of novel non-cytolytic antiviral factors derived from CD8+ T cells of HIV-infected individuals using the ProteinChip® system

Collaborator
Crucell

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Development of an improved recombinant adenovirus vector for vaccination against the Ebola virus

Collaborator
Genetics Institute

Investigators
Stephen Straus, M.D.
Warren Strober, M.D.
Peter Mannon, M.D.
Ivan Fuss, M.D.
Laboratory of Clinical Investigation

Title
A randomized, double-blind, placebo-controlled, dose-finding, safety study of two parallel dose levels of subcutaneously administered human monoclonal antibody to interleukin-12 (J695) in patients with active Crohn's disease

Collaborator
GenVec

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Evaluation of adenoviral vectors encoding HIV-1 proteins

Collaborator
GlaxoSmithKline

Investigators
Holli Hamilton, M.D., M.P.H.
Barbara Savarese, R.N.
Division of Microbiology and Infectious Diseases

Title
A double-blind, randomized, controlled phase III study to assess the prophylactic efficacy of rgD/Alum/MPL vaccine in the prevention of genital herpes disease in young sexually active women

Collaborator
Ichor Medical Systems

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Evaluation of electroporation-mediated delivery of an HIV DNA vaccine

Collaborator
Maxygen

Investigator
Louis Miller, M.D.
Laboratory of Parasitic Diseases

Title
Novel, polyspecific malaria vaccine development based on PfEMP1 using MolecularBreeding™ directed molecular evolution technologies

Collaborator
Merial

Investigator
Jose Ribeiro, M.D.
Laboratory of Parasitic Diseases

Title
Evaluation of DNA vaccines encoding sand fly salivary proteins as candidates to control *Leishmania infantum* infection in dogs

CRADAs in Effect, FY 2002

Collaborator
Achillion Pharmaceuticals

Investigators
John Inman, Ph.D.
Laboratory of Immunology
Ettore Appella, M.D.
National Cancer Institute

Title
Development of optimized inhibitors of protein zinc finger domains

Collaborator
American Cyanamid

Investigator
Brian Murphy, M.D.
Laboratory of Infectious Diseases

Title
Development of safe and effective live-attenuated vaccines for respiratory syncytial virus subgroups A and B and parainfluenza viruses type 1, 2, and 3

Collaborator
American Home Products

Investigator
Jeffrey Cohen, M.D.
Laboratory of Clinical Investigation

Title
Identification of varicella-zoster gene targets

Collaborator
Aviron

Investigator
Ann Ginsberg, M.D., Ph.D.
Division of Microbiology and Infectious Diseases

Title
Development of a live, attenuated cold-adapted influenza vaccine

Collaborator
Biospace.com

Investigator
Laurence Wolfe, Ph.D.
Office of Technology and Information Systems

Title
Development of an electronic procurement system for commodity identification, product and service acquisition, and budget tracking

Collaborator
Chiron

Investigator
H. Clifford Lane, M.D.
Laboratory of Immunoregulation

Title
Research and development of interleukin-2 as a treatment for HIV infection

Collaborator
Ciphergen Biosystems

Investigators
John Kehrl, M.D.
Tae-Wook Chun, Ph.D.
Laboratory of Immunoregulation

Title
Identification and characterization of novel non-cytolytic antiviral factors derived from CD8+ T cells of HIV-infected individuals using the ProteinChip® system

Collaborator
Connaught Technology

Investigator
Warren Strober, M.D.
Laboratory of Clinical Investigation

Title
Development of vectored vaccines and therapeutics for the prevention and treatment of AIDS

Collaborator
Crucell

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Development of an improved recombinant adenovirus vector for vaccination against the Ebola virus

Collaborator
Genetics Institute

Investigator
Ethan Shevach, M.D.
Laboratory of Immunology

Title
Analysis of gene expression in immunoregulatory T cells that co-express the CD4 and CD25 surface markers

Collaborator
Genetics Institute

Investigators
Stephen Straus, M.D.
Warren Strober, M.D.
Peter Mannon, M.D.
Ivan Fuss, M.D.
Laboratory of Clinical Investigation

Title
A randomized, double-blind, placebo-controlled, dose-finding, safety study of two parallel dose levels of subcutaneously administered human monoclonal antibody to interleukin-12 (J695) in patients with active Crohn's disease

Collaborator
Genetics Institute

Investigator
Thomas Wynn, Ph.D.
Laboratory of Parasitic Disease

Title
Development of interleukin-13 antagonism as a treatment for fibrosis in schistosomiasis

Collaborator
GenVec

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Evaluation of adenoviral vectors encoding HIV-1 proteins

Collaborator
Genzyme Transgenics

Investigators
B. Fenton "Lee" Hall, M.D., Ph.D.
David Kaslow, M.D.
Division of Microbiology and Infectious Diseases

Title
Transgenic malaria vaccines: process development, preclinical, and initial clinical evaluation

Collaborator
GlaxoSmithKline

Investigator
Clifton Barry, Ph.D.
Laboratory of Immunogenetics

Title
Development of new drugs for the treatment of tuberculosis

Collaborator
GlaxoSmithKline

Investigators
Holli Hamilton, M.D., M.P.H.
Barbara Savarese, R.N.
Division of Microbiology and Infectious Diseases

Title
A double-blind, randomized, controlled phase III study to assess the prophylactic efficacy of rgD/Alum/MPL vaccine in the prevention of genital herpes disease in young sexually active women

Collaborator
GlaxoSmithKline

Investigator
David Klein, Ph.D.
Division of Microbiology and Infectious Diseases

Title
Adult pertussis vaccine

Collaborator
GlaxoSmithKline

Investigator
Robert H. Purcell, M.D.
Laboratory of Infectious Diseases

Title
Hepatitis C vaccine

Collaborator
GlaxoSmithKline

Investigator
Robert H. Purcell, M.D.
Laboratory of Infectious Diseases

Title
Hepatitis E vaccine

Collaborator
Hong Kong Institute of Biotechnology

Investigator
Louis Miller, M.D.
Laboratory of Parasitic Diseases

Title
Process development, scale-up, manufacturing, and initial clinical testing of a recombinant subunit malaria vaccine produced in yeast

Collaborator
Ichor Medical Systems

Investigator
Phillip Gomez, Ph.D.
Vaccine Research Center

Title
Evaluation of electroporation-mediated delivery of an HIV DNA vaccine

Collaborator
Lederle-Praxis Biologicals

Investigator
Peter Collins, Ph.D.
Laboratory of Infectious Diseases

Title
Production of live attenuated RSV and PIV vaccine viruses from cDNA

Collaborator
Lederle-Praxis Biologicals

Investigators
Mark Connors, M.D.
Laboratory of Immunoregulation
Marjorie Robert-Guroff, Ph.D.
National Cancer Institute

Title
HIV recombinants—development of HIV vaccine

Collaborator
LigoCyte Pharmaceuticals

Investigator
Donald Lodmell, Ph.D.
Laboratory of Persistent Viral Diseases

Title
Mucosal vaccination of mice using an M-cell targeted adhesion protein-rabies DNA vaccine construct

Collaborator
Maxygen

Investigator
Louis Miller, M.D.
Laboratory of Parasitic Diseases

Title
Novel, polyspecific malaria vaccine development based on PfEMP1 using MolecularBreeding™ directed molecular evolution technologies

Collaborator
Merck

Investigator
Gary Nabel, M.D., Ph.D.
Vaccine Research Center

Title
Development of an adenoviral-based HIV vaccine

Collaborator
Merck

Investigator
Stephen Straus, M.D.
Laboratory of Clinical Investigation

Title
A double-blind, placebo-controlled study of the efficacy of live, attenuated Oka/Merck varicella-zoster vaccine in reducing the incidence and/or severity of shingles in adults

Collaborator
Merial

Investigator
Jose Ribeiro, M.D.
Laboratory of Parasitic Diseases

Title
Evaluation of DNA vaccines encoding sand fly salivary proteins as candidates to control *Leishmania infantum* infection in dogs

Collaborator
Nexell Therapeutics

Investigators
Harry L. Malech, M.D.
Mitchell Horwitz, M.D.
Laboratory of Host Defenses

Title
Study of low-intensity preparative regimen followed by HLA-matched transplantation for chronic disease

Collaborator
Novartis

Investigator
Marshall Plaut, M.D.
Division of Allergy, Immunology and Transplantation

Title
A double-blind, placebo-controlled study of the efficiency of E25 anti-IgE reducing asthma symptoms in inner-city children

Collaborator
Novavax

Investigator
Louis Miller, M.D.
Laboratory of Parasitic Diseases

Title
Merozoite surface protein 1 expressed in insect cells: process development, preclinical, and initial clinical evaluation

Collaborator
Pharmacopeia

Investigator
Clifton Barry, Ph.D.
Laboratory of Immunogenetics

Title
Screening *Mycobacterium tuberculosis*

Collaborator
Protein Design Labs

Investigators
Catherine Laughlin, Ph.D.
Stephen Straus, M.D.
Division of Microbiology and Infectious Diseases

Title
Production and clinical evaluation of human anti-herpes simplex virus (HSV) monoclonal antibody as a therapeutic agent for the treatment of neonatal HSV infections

Collaborator
RAMS, Inc.

Investigators
John McGowan, Ph.D.
Division of Extramural Activities
Alexander Rosenthal
Center for Information Technology

Title
Development of integrated systems

Collaborator
Sequella

Investigator
Clifton Barry, Ph.D.
Laboratory of Immunogenetics

Title
High synthesis and screening

Collaborator
Wyeth-Lederle Vaccines

Investigator
Pamela McInnes, Ph.D.
Division of Microbiology and
Infectious Diseases

Title
Preventing childhood mortality—an efficacy trial of a pneumococcal conjugate vaccine in upper and central river divisions, The Gambia

NIH EXTRAMURAL FUNDING MECHANISMS USED BY NIAID

F31 Predoctoral Individual National Research Service Award (NRSA)—provides predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

F32 Postdoctoral Individual NRSA—provides postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

F33 NRSA for Senior Fellows—provides opportunities for experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, or to acquire new research capabilities.

F35 Intramural NRSA Individual Postdoctoral Program—supports a postdoctoral trainee in the NIH intramural program.

K02 Independent Scientist Award—provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.

K08 Clinical Investigator Award—provides the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who will pursue research aspects of categorical areas applicable to the awarding unit, and aids in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.

K22 Career Transition Award—provides support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two-phase program: an initial period involving an intramural appointment of the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator to sustain or promote a successful research career.

K23 Mentored Patient-Oriented Research Career Development Award—provides support for the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a 3-year minimum up to a 5-year period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators.

K24 Midcareer Investigator Award in Patient-Oriented Research—provides support for experienced clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators.

K25 Mentored Quantitative Research Career Development Award—supports junior-faculty-level investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who have the potential to integrate their expertise with biomedicine and to develop into productive investigators with a period of mentored study and research.

K30 Clinical Research Curriculum Award (CRCA)—awarded to institutions to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. This award is intended to support the development of new didactic programs in clinical research at institutions that do not currently offer such programs or in institutions with existing didactic programs in clinical research to support or expand their programs or to improve the quality of instruction.

N01 Research and Development Contract—develops or applies new knowledge or tests, screens or evaluates a product, material, device, or component for use by the scientific community.

P01 Research Program Project—provides a qualified institution on behalf of a principal investigator with the support of a broadbased, multidisciplinary, often long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources necessary for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

P30 Center Core Grant—supports shared resources and facilities for categorical research by a number of investigators from different disciplines who provide a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem. Although funded independently of the center's component projects or program projects, the core grant relates integratively to them. By providing more accessible resources, this support is expected to ensure greater productivity than that obtained from the separate projects and program projects.

P50 Specialized Center—supports any part of the full range of R&D, from basic to clinical, and may involve ancillary supportive activities, such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical problem area. These grants differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers also may serve as regional or national resources for special research purposes.

R01 Research Project Grant (traditional)—provides support to an institution (domestic or foreign) on behalf of a principal investigator for a discrete project related to the investigator's interests and competence. Most of the research that the NIH supports is maintained through this funding mechanism. Although rare, such a grant may be awarded directly to an individual.

R03 Small Grant—provides research support specifically limited in time and amount for studies in categorical program areas.

Small grants provide flexibility for initiating studies, which are generally for preliminary short-term projects and are nonrenewable.

R09 Scientific Evaluation—provides the chairman of an initial review group funds for operation of the initial review group.

R13 Conference Grant—provides funding for conferences to coordinate, exchange, and disseminate information related to program interests. In general, such awards are modest and limited to participation with other organizations in the support of conferences rather than as a provision of sole support. Among the costs eligible for support are salaries, equipment rental, travel, consultant services, and supplies. Prospective applicants should inquire in advance concerning possible interest on the part of an Institute.

R15 Academic Research Enhancement Award (AREA)—provides support to scientists at eligible domestic institutions for small-scale, new, or expanded health-related research projects, such as pilot research projects and feasibility studies; development, testing, and refinement of research techniques; secondary analysis of available data sets; and similar discrete research projects that demonstrate research capability. This award is directed toward smaller, less-prominent 4-year public and private colleges and universities that provide undergraduate training for a significant number of U.S. research scientists but have not had an adequate share in the growth of the NIH extramural program.

R18 Research Demonstration and Dissemination Project—provides support to develop, test, and evaluate health-service activities and to foster the application of existing knowledge for the control of categorical diseases.

R21 Exploratory/Developmental Grant—used by NIAID for bridge awards. The bridge award provides support for a limited time and amount to investigators to enable them to continue meritorious research and improve the competitiveness of future grant applications.

R24 Resource-Related Research Project—supports research projects that will enhance the capability of resources to serve biomedical research.

R25 Education Project—provides support to develop or implement a program in education, information, training, technical assistance, coordination, or evaluation.

R33 Exploratory and Developmental Grants, Phase II—provide a second phase of support for innovative, exploratory, and developmental research begun as an R21 award. Only R21 awardees are eligible to apply for R33 support. Applications are accepted only in response to RFAs and PAs that specify the R33 mechanism.

R37 Method to Extend Research in Time (MERIT) Award—provides long-term, stable support to investigators who are likely to continue to perform in an outstanding manner and spares them the administrative burdens associated with preparing and submitting research grant applications. An initial 5-year award is accompanied by an opportunity for a 3- to 5-year extension, based on an

expedited review of the accomplishments during the initial award period. Investigators may not apply for a MERIT award. NIH staff and advisors base their selection of MERIT award recipients on competing R01 applications, prepared and submitted in accordance with NIH procedures. MERIT awards are awarded to a limited number of selected investigators who have demonstrated superior competence and outstanding productivity during previous research endeavors.

R41 Small Business Technology Transfer
R42 (STTR) Grants—support cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.

R43 Small Business Innovation Research
R44 (SBIR) Grants—enable small businesses possessing technological expertise to contribute to the R&D mission of the NIH. Phase I (R43) grants support projects, limited in time and amount, to establish the technical merit and feasibility of R&D ideas that ultimately may lead to commercial products or services. Phase II (R44) grants support in-depth development of R&D ideas whose feasibility has been established in phase I and that are likely to result in commercial products or services. The research must be conducted in the United States.

T32 Institutional NRSA—enables institutions to grant NRSAs for predoctoral and postdoctoral research training in specified shortage areas to individuals selected by the institutions.

T35 NRSA Short-Term Research Training—provides individuals with research training during off-quarters or summer periods to encourage research careers or research in areas of national need.

U01 Research Project (Cooperative Agreement)—provides an assistance relationship between the NIH and a recipient, but with substantial programmatic involvement by the NIH. The NIH assists, supports, or stimulates the recipients and is involved substantially with recipients in conducting projects similar in program content to those for grants, with the NIH playing a "partner" role in the effort.

U19 Research Program (Cooperative Agreement)—supports a research program of multiple projects directed toward a specific major objective, basic theme, or program goal that requires a broadbased, multidisciplinary, and often long-term approach.

U24 Resource-Related Research Projects/Cooperative Agreements—support research projects contributing to improvement of the capability of resources to serve biomedical research.

U42 Animal (Mammalian and Nonmammalian) Model and Animal and Biomedical Materials Resource Cooperative Agreements (NCRR)—develop and support an animal (mammalian and nonmammalian) model or animal or biological materials resources available to all qualified

investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program. Nonmammalian resources include nonmammalian vertebrates, invertebrates, cell systems, and nonbiological systems.

U54 Specialized Centers Cooperative Agreements—support research and development from basic to clinical, including ancillary supportive activities that create a multidisciplinary focus on a disease or a biomedical problem. Centers may also serve as regional or national resources for special research purposes.

U56 Exploratory Grants Cooperative Agreements—support planning for new programs, expansion or modification of existing resources, and feasibility studies for interdisciplinary programs that may lead to specialized or comprehensive centers.

UC1 NIH Challenge Grants and Partnerships Program, Phase II, Cooperative Agreements (NIAID)—promote joint ventures between the NIH and both domestic and global entities to facilitate rapid biomedical or biotechnology R&D for infectious diseases to benefit public health; projects should have a commercial potential that could not have been attained without matching funds.

Y01 NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides a source of funds to another Federal organization outside DHHS to acquire specific products, services, or studies.

Y02 NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides funds to another NIH component or to another organization within DHHS to acquire specific products, services, or studies.

ACRONYMS

AACTG	Adult AIDS Clinical Trials Group
AADRC	Asthma and Allergic Diseases Research Center
ABC	Actions for Building Capacity
ACE	Autoimmunity Centers of Excellence
ADCC	Autoimmune Diseases Coordinating Committee
ADMO	Associate Director for Management and Operations
AIDS	acquired immunodeficiency syndrome
AIEDRP	Acute HIV Infection and Early Disease Research Program
AIT	allergen immunotherapy
ALT	alanine aminotransferase
AREA	Academic Research Enhancement Award
ART	antiretroviral therapy
ATCC	American Type Culture Collection
AVRWG	AIDS Vaccine Research Working Group
BAMBU	Bacteriology and Mycology Biostatistical Unit
BAMSG	Bacteriology and Mycology Study Group
BISC	Bioinformatics Integration Support Contract
BSC	Board of Scientific Counselors
BSE	bovine spongiform encephalopathy or “mad cow” disease
BSL-3	biosafety-level-three
BTEP	BioTechnology Engagement Program
CASG	Collaborative Antiviral Study Group
CCTAT	Cooperative Clinical Trials in Adult Kidney Transplantation
CCTPT	Cooperative Clinical Trials in Pediatric Kidney Transplantation
CDA	Confidential Disclosure Agreement
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Program for Research on AIDS

CJD	Creutzfeldt-Jakob Disease
CMB	Contract Management Branch
CMV	cytomegalovirus
CPCRA	Terry Beirn Community Programs for Clinical Research on AIDS
CRADA	Cooperative Research and Development Agreement
CRC	Cooperative Research Center
CRCA	Clinical Research Curriculum Award
CRDF	Civilian Research and Development Foundation
CTA	Clinical Trial Agreement
CTL	cytotoxic T lymphocyte
CWD	chronic wasting disease
DAIDS	Division of Acquired Immunodeficiency Syndrome, NIAID
DAIT	Division of Allergy, Immunology and Transplantation, NIAID
DARPA	Defense Advanced Research Projects Agency
DEA	Division of Extramural Activities, NIAID
DEN4	dengue virus type 4
DHHS	U.S. Department of Health and Human Services
DIR	Division of Intramural Research, NIAID
DMID	Division of Microbiology and Infectious Diseases, NIAID
DNA	deoxyribonucleic acid
DSA	Drug Screening Agreement
EF	edema factor
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FIC	Fogarty International Center
FOIA	Freedom of Information Act
FY	fiscal year
GAVI	Global Alliance for Vaccines and Immunization

GP	glycoprotein
GSK	GlaxoSmithKline
HAART	highly active antiretroviral therapy
HBV	hepatitus B virus
HC CRCs	Hepatitis C Cooperative Research Centers
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HOPE	Health Omnibus Programs Extension
HPIV3	human parainfluenza type 3
HPTN	HIV Prevention Trials Network
HPV	human papilloma virus
HSV	herpes simplex virus
HVDDT	HIV Vaccine Design and Development Teams
HVTN	HIV Vaccine Trials Network
ICBG	International Cooperative Biodiversity Groups Program
ICER	International Center for Excellence in Research
ICIDR	International Collaboration in Infectious Disease Research
ICS	Institutes and Centers
ICTDR	International Centers for Tropical Disease Research
IDF	Immune Deficiency Foundation
IHWG	International Histocompatibility Working Group
IL-4	interleukin-4
IND	investigational new drug
IOM	Institute of Medicine
IPCP	Integrated Preclinical/Clinical Program
ITN	Immune Tolerance Network
JDRF	Juvenile Diabetes Research Foundation International

JEV	Japanese encephalitis virus
KNCV	Royal Netherlands TB Association
LF	lethal factor
MACS	Multicenter AIDS Cohort Study
MADGC	Multiple Autoimmune Disease Genetics Consortium
MDR-TB	multi-drug-resistant tuberculosis
MERIT	Method to Extend Research in Time
MGC	Mammalian Gene Collection
MHC	major histocompatibility complex
MIM	Multilateral Initiative on Malaria
MR4	Malaria Research and Reference Reagent Resource
MRSA	methicillin-resistant Staphylococcus aureus
MRTC	Malaria Research and Training Center
MSG	Mycoses Study Group
MTA	Material Transfer Agreement
Mtb	mycobacterium tuberculosis
MTCT	mother-to-child transmission
MVA	modified vaccinia virus Ankara
MVDU	Malaria Vaccine Development Unit
NAAIDC	National Advisory Allergy and Infectious Diseases Council
NARAC	North American Rheumatoid Arthritis Consortium
NARSA	Network on Antimicrobial Resistance in Staphylococcus aureus
NCICAS	National Cooperative Inner-City Asthma Study
NCRR	National Center for Research Resources
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NRSA	National Research Service Award
NVPO	National Vaccine Program Office
OAS	Office of Administrative Services, NIAID
OCPL	Office of Communications and Public Liaison, NIAID
OCR	Office of Clinical Research, NIAID
OD	Office of the Director, NIAID
OE	Office of Ethics, NIAID
OFM	Office of Financial Management, NIAID
OHRM	Office of Human Resources Management, NIAID
OI	opportunistic infection
OMNI	Office of Management for New Initiatives, NIAID
OPA	Office of Policy Analysis, NIAID
OSPRT	Office of Special Populations and Research Training, NIAID
OTD	Office of Technology Development, NIAID
OTIS	Office of Technology Information Systems, NIAID
OTT	Office of Technology Transfer, NIH
PA	protective antigen
PACTG	Pediatric AIDS Clinical Trials Group
PFGRC	Pathogen Functional Genomics Resource Center
PID	pelvic inflammatory disease
PIDR	Primary Immunodeficiency Diseases Registry
PIV	parainfluenza virus
PMPA	phosphonylmethoxypropyl adenine
PR	protease
PrP	prion protein
PRP	polyribosylribose phosphate

R&D	research and development
RFA	request for application
RML	Rocky Mountain Laboratories
RPAB	Referral and Program Analysis Branch
RPG	research project grant
RSV	respiratory syncytial virus
RT	reverse transcriptase
SAIC	Science Applications International Corporation
SBIR	Small Business Innovation Research
SCID	severe combined immunodeficiency disease
SIV	simian immunodeficiency virus
SLE	systemic lupus erythematosus
SLEV	St. Louis encephalitis virus
SMART	Strategies for Management of Anti-Retroviral Therapies
SNP	single nucleotide polymorphisms
SPR	Summer Program Review
SRP	Scientific Review Program
STD	sexually transmitted disease
STTR	Small Business Technology Transfer
SVEU	Simian Vaccine Evaluation Unit
TB	tuberculosis
TBRU	Tuberculosis Research Unit
TDRU	Tropical Disease Research Unit
TEAC	Technology Evaluation Advisory Committee
TMRC	Tropical Medicine Research Center
TSE	transmissible spongiform encephalopathy
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMRMC	U.S. Army Medical Research and Material Command
USJCMSP	U.S.-Japan Cooperative Medical Science Program

VAP	Vaccine Action Program
VDF	Vaccine Development Facility
VPP	Vaccine Pilot Plant
VRC	The Dale and Betty Bumpers Vaccine Research Center
VRE	vancomycin-resistant enterococci
VTEU	Vaccine and Treatment Evaluation Unit
WHO	World Health Organization..
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WNV	West Nile virus
WPR	Winter Policy Retreat
YFV	yellow fever virus

INDEX

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Y

DIRECTORY OF NIAID PERSONNEL[a]

OFFICE OF THE DIRECTOR (OD)	Bldg.[b]	Room	Phone	E-mail
Anthony S. Fauci, M.D., *Director*	31	7A03	(301) 496-2263	af10r@nih.gov
John R. La Montagne, Ph.D., *Deputy Director*	31	7A03	(301) 496-9677	jm79q@nih.gov
Mark Dybul, M.D., *Assistant Director for Medical Affairs*	31	7A03	(301) 496-2263	md129j@nih.gov
Elizabeth A. Fleming, *Special Concerns Program Officer*	6700B	3122	(301) 496-1012	bf38c@nih.gov
Gregory K. Folkers, *Senior Public Affairs Advisor*	31	7A03	(301) 496-2263	gfolkers@nih.gov
Jack Killen, *Assistant Director for Biodefense Research*	31	7A28	(301) 451-4262	jkillen@niaid.nih.gov
Margaret A. Moore, *Special Assistant to the Director*	31	7A03	(301) 496-9118	mm52s@nih.gov
Karl A. Western, M.D., D.T.P.H., *Assistant Director for International Research*	6700B	3154	(301) 496-6721	kw18g@nih.gov
OFFICE OF CLINICAL RESEARCH (OCR)				
H. Clifford Lane, M.D., *Director*	10	11S231	(301) 496-7196	cl17d@nih.gov
OFFICE OF ETHICS (OE)				
Karen Santoro, J.D., *Director*	6610	4019	(301) 435-6542	ks@niaid.nih.gov
ASSOCIATE DIRECTOR FOR MANAGEMENT AND OPERATIONS (ADMO)				
Lynn C. Hellinger, *Associate Director for Management and Operations*	31	7A16	(301) 594-3964	lh28q@nih.gov
Roger E. Pellis, *Executive Officer*	31	7A05	(301) 496-9205	rp16r@nih.gov
Office of Administrative Services (OAS)				
Roger E. Pellis, *Director*	31	7A05	(301) 496-9205	rp16r@nih.gov
Acquisition Management and Operations Branch (AMOB)				
Rebecca A. Guenther, *Chief*	6700B	1131	(301) 402-2284	rg45t@nih.gov
Extramural Administrative Management Branch (EAMB)				
Marilyn E. Kunzweiler, *Chief*	6700B	1140	(301) 496-7151	mk34g@nih.gov
Intramural Administrative Management Branch (IAMB)				
Ekaterini (Katy) Perry, *Chief*	10	4A26	(301) 496-7089	kperry@niaid.nih.gov
Management Services Branch (MSB)				
Susan Cook, *Chief*	31	7A19	(301) 496-1521	sc67r@nih.gov
Office of Communications and Public Liaison (OCPL)				
Laurie Doepel, *Acting Director*	31	7A50	(301) 496-5717	ldoepel@niaid.nih.gov
Office of Financial Management (OFM)				
Ralph Tate, *Director*	31	7A08	(301) 496-4701	rtate@niaid.nih.gov
Office of Human Resources Management (OHRM)				
Elizabeth A. Holmes, *Acting Director*	31	7A20	(301) 496-9686	eh13a@nih.gov
Office of Management for New Initiatives (OMNI)				
Richard Freed, *Director*	Dmc2	Ste. 880	(301) 451-4328	rf99f@nih.gov

	BLDG.	ROOM	PHONE	E-MAIL
Office of Policy Analysis (OPA)				
Nancy Blustein, *Director*	31	7A16	(301) 496-6752	nblustein@niaid.nih.gov
Office of Technology Development (OTD)				
Michael Mowatt, Ph.D., *Director*	6610	4035	(301) 496-2644	mm25q@nih.gov
Office of Technology Information Systems (OTIS)				
Laurence B. Wolfe, Ph.D., *Director*	31	7A32	(301) 496-8219	lw14w@nih.gov
Extramural Network Systems Branch (ENSB)				
Kim L. Kassing, *Chief*	6700B	4124	(301) 402-3580	kk15w@nih.gov
Intramural Technical Systems Branch (ITSB)				
Timothy P. Barnes, *Chief*	10	4A30A	(301) 496-0205	tb3h@nih.gov
Management Information Systems Branch (MISB)				
Michael Tartakovsky, *Chief*	6700B	4116	(301) 594-3414	mt92q@nih.gov
DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER (VRC)				
Gary J. Nabel, M.D., Ph.D., *Director*	40	4502	(301) 496-1852	gn34v@nih.gov
John Mascola, M.D., *Deputy Director*	40	5512	(301) 594-8490	jm557m@nih.gov
Abe Mittelman, *Associate Director for Management and Operations*	40	1120	(301) 594-8493	amittelm@mail.nih.gov
Laboratory of Clinical Trials (LCT)				
Barney S. Graham, M.D., *Senior Investigator*	40	2502	(301) 594-8513	bg118j@nih.gov
Laboratory of Immunology (LI)				
Richard Koup, M.D., *Senior Investigator*	40	3502	(301) 594-8585	rk173f@nih.gov
Laboratory of Vaccine Production (LVP)				
Phillip Gomez III, Ph.D., *Senior Investigator*	40	5502	(301) 594-8485	pgomez@nih.gov
Laboratory of Viral Pathogenesis (LVP)				
Barney S. Graham, M.D., *Senior Investigator*	40	2502	(301) 594-8513	bg118j@nih.gov
Laboratory of Virology (LV)				
Gary J. Nabel, M.D., Ph.D., *Senior Investigator*	40	4502	(301) 496-1852	gnabel@nih.gov
DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME (DAIDS)				
Edward C. Tramont, M.D., *Director*	6700B	4142	(301) 496-0545	etramont@niaid.nih.gov
Jonathan M. Kagan, Ph.D., *Deputy Director*	6700B	4140	(301) 496-0545	jk38m@nih.gov
Office of Program Operations and Scientific Information (OPOSI)				
Matthew Murguia, *Associate Director*	6700B	4143	(301) 496-0545	murguia@niaid.nih.gov
Office of Clinical Research Policy and Resources (OCRPR)				
Vacant, *Associate Director*	6700B			
Pharmaceutical Affairs Branch (PAB)				
Ana I. Martinez, Ph.D., *Chief*	6700B	5115	(301) 496-8213	am30c@nih.gov

	BLDG.	ROOM	PHONE	E-MAIL
Regulatory Affairs Branch (RAB)				
MaryAnne Luzar, Ph.D., *Chief*	6700B	5114	(301) 435-3741	ml29g@nih.gov
Basic Sciences Program (BSP)				
Carl W. Dieffenbach, Ph.D., *Associate Director*	6700B	4133	(301) 496-0637	cd17u@nih.gov
Epidemiology Branch (EB)				
Vacant, *Chief*	6700B	4132	(301) 402-0135	
Pathogenesis and Basic Research Branch (PBRB)				
Susan F. Plaeger, Ph.D., *Chief*	6700B	4134	(301) 496-8378	splaeger@niaid.nih.gov
Targeted Interventions Branch (TIB)				
Sandra Bridges, Ph.D., *Chief*	6700B	4128	(301) 496-8198	sbridges@niaid.nih.gov
Therapeutics Research Program (TRP)				
Frederick Batzold, Ph.D. *Acting Associate Director*	6700B	5101	(301) 496-8210	fb10c@nih.gov
Clinical Research Management Branch (CRMB)				
Margaret Matula, B.S.N., M.G.A. *Acting Chief*	6700B	5153	(301) 402-2302	mmatula@niaid.nih.gov
Drug Development and Clinical Sciences Branch (DDCSB)				
Michael Ussery, *Chief*	6700B	5150	(301) 496-0636	mussery@niaid.nih.gov
HIV Research Branch (HIVRB)				
Carla B. Pettinelli, M.D., Ph.D., *Chief*	6700B	5102	(301) 496-0700	cp22n@nih.gov
Complications and Co-Infections Research Branch (CCRB)				
Barbara E. Laughon, Ph.D., *Chief*	6700B	5108	(301) 402-2304	bl17u@nih.gov
Pediatric Medicine Branch (PMB)				
James G. McNamara, M.D., *Chief*	6700B	5106	(301) 402-2300	jm74q@nih.gov
Vaccine and Prevention Research Program (VPRP)				
Margaret I. Johnston, Ph.D., *Associate Director*	6700B	4101	(301) 402-0846	pj7p@nih.gov
Preclinical Research and Development Branch (PRDB)				
James Bradac, Ph.D., *Chief*	6700B	4102	(301) 402-0121	jb68k@nih.gov
Prevention Sciences Branch (PSB)				
Kevin Ryan, Ph.D., *Chief*	6700B	4109	(301) 435-8896	kryan@niaid.nih.gov
Vaccine Clinical Research Branch (VCRB)				
Jorge E. Flores, M.D., *Chief*	6700B	4154	(301) 496-8200	jf30t@nih.gov
DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION (DAIT)				
Daniel Rotrosen, M.D., *Director*	6700B	5142	(301) 496-1886	dr17g@nih.gov
William Duncan, Ph.D., *Deputy Director*	6700B	5134	(301) 496-1886	wduncan@niaid.nih.gov
Office of Clinical Applications (OCA)				
William Duncan, Ph.D., *Acting Director*	6700B	5130	(301) 496-1886	wduncan@niaid.nih.gov
Office of Epidemiology and Clinical Trials (OECT)				
Capt. Ernestine T. Smartt, R.N., *Director*	6700B	5145	(301) 496-7353	es23r@nih.gov
Office of Program Planning, Operations, and Scientific Information (OPOSI)				
Jean McKay, *Director*	6700B	5137	(301) 496-1886	jmckay@niaid.nih.gov
Carole Cole, *Deputy Director*	6700B	5137	(301) 496-1886	ccole@niaid.nih.gov
Asthma, Allergy, and Inflammation Branch (AAIB)				
Vacant, *Chief*	6700B	5141	(301) 496-8973	

	BLDG.	ROOM	PHONE	E-MAIL
Basic Immunology Branch (BIB)				
Helen R. Quill, Ph.D., *Chief*	6700B	5140	(301) 496-7551	hq1t@nih.gov
Clinical Immunology Branch (CIB)				
William Duncan, Ph.D., *Acting Chief*	6700B	5135	(301) 496-1886	wduncan@niaid.nih.gov
Transplantation Immunobiology Branch (TIB)				
Shiv Prasad, Ph.D., *Chief*	6700B	5130	(301) 496-5598	sp89j@nih.gov
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID)				
Carole A. Heilman, Ph.D., *Director*	6700B	3142	(301) 496-1884	ch25v@nih.gov
Pamela M. McInnes, D.D.S., *Deputy Director*	6700B	3143	(301) 496-1884	pm23m@nih.gov
Robert L. Quackenbush, Ph.D., *Assistant Director for Research Training Referral and Minority Affairs*	6700B	3147	(301) 496-1884	rq1i@nih.gov
Office of Biodefense Research Activities				
Ernie Takafuji, M.D., Ph.D., *Director*	6610	5111	(301) 402-4197	etakafuji@niaid.nih.gov
Office of Clinical Research Affairs (OCRA)				
Holli Hamilton, *Chief*	6700B	3120	(301) 496-7067	hh88f@nih.gov
Office of Regulatory Affairs (ORA)				
Lydia Falk, *Director*	6700B	3138	(301) 402-2126	lf116u@nih.gov
Office of Scientific Coordination and Program Operations (OSCPO)				
Irene Glowinski, Ph.D., *Chief*	6700B	3139	(301) 496-1884	ig2v@nih.gov
Bacteriology and Mycology Branch (BMB)				
Dennis M. Dixon, Ph.D., *Chief*	6610	4111	(301) 496-7728	dd24a@nih.gov
Enteric and Hepatic Diseases Branch (EHDB)				
Leslye D. Johnson, Ph.D., *Chief*	6700B	3109	(301) 496-7051	lj7m@nih.gov
Parasitology and International Programs Branch (PIPB)				
Michael Gottlieb, Ph.D., *Chief*	6610	4015	(301) 496-2544	mg35s@nih.gov
Respiratory Diseases Branch (RDB)				
Pamela M. McInnes, D.D.S., *Acting Chief*	6700B	3143	(301) 496-5305	ag73i@nih.gov
Sexually Transmitted Diseases Branch (STDB)				
Carolyn Deal, Ph.D., *Chief*	6610	5039	(301) 496-1884	cdeal@niaid.nih.gov
Virology Branch (VB)				
Catherine A. Laughlin, Ph.D., *Chief*	6610	4409	(301) 496-7453	cl28r@nih.gov
DIVISION OF EXTRAMURAL ACTIVITIES (DEA)				
John J. McGowan, Ph.D., *Director*	6700B	2142	(301) 496-7291	jm80c@nih.gov
Allan W. Czarra, *Deputy Director*	6700B	2144	(301) 496-7291	ac20a@nih.gov
Maya Hadar, *Special Assistant to the Director*	6700B	2138	(301) 496-7291	mh31y@nih.gov
Claudia R. Goad, *Committee Management Officer*	6700B	2147	(301) 496-7601	cg22w@nih.gov
Gregory Milman, Ph.D., *Director, Office of Innovation and Special Programs, SBIR Programs and Division Operations*	6700B	2140	(301) 496-7291	gm162@nih.gov
Office of Program Coordination and Operations (OPCO)				
Allan W. Czarra, *Director*	6700B	2144	(301) 496-7291	ac20a@nih.gov
Office of Special Populations and Research Training (OSPRT)				
Milton J. Hernandez, Ph.D., *Director*	6700B	2133	(301) 496-8697	mh35c@nih.gov

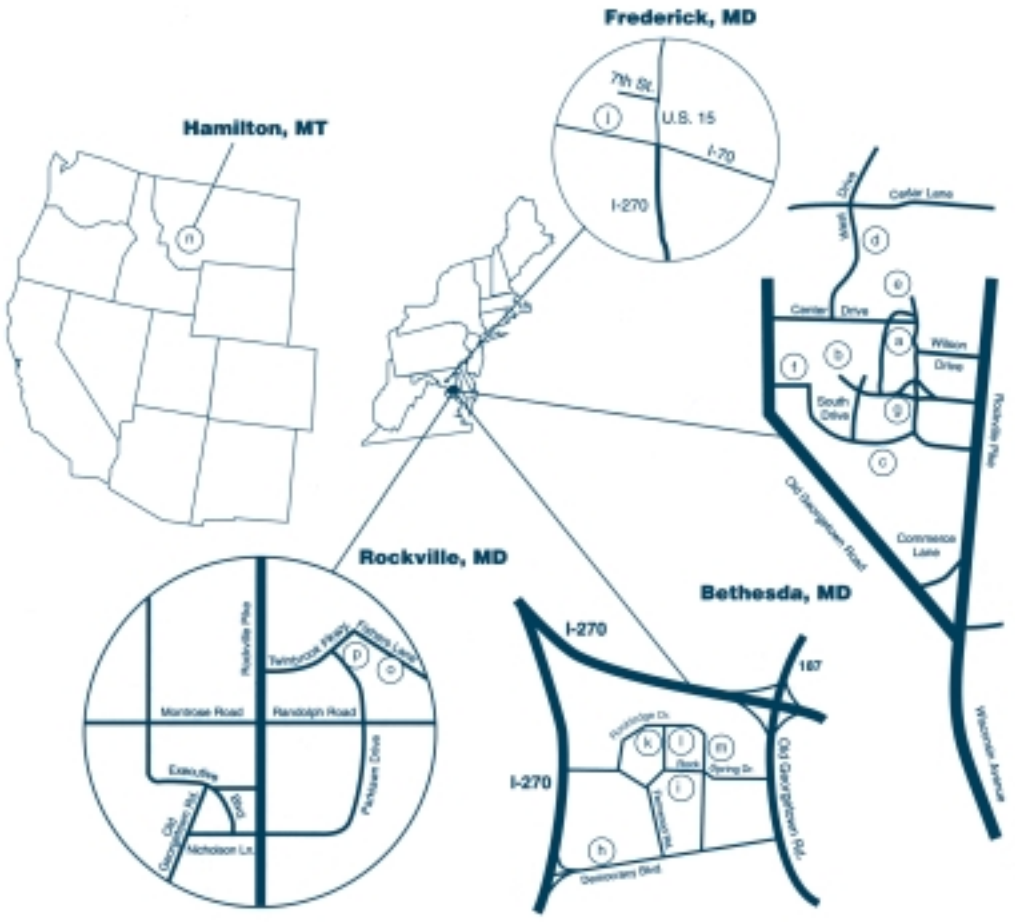
	BLDG.	ROOM	PHONE	E-MAIL
Contract Management Branch (CMB)				
Brenda J. Velez, *Chief*	6700B	2115	(301) 496-0612	bv4y@nih.gov
Grants Management Branch (GMB)				
Mary C. Kirker, *Chief*	6700B	2116	(301) 496-7075	mk35h@nih.gov
Referral and Program Analysis Branch (RPAB)				
Lai S. Tan, *Chief*	6700B	2134	(301) 496-5318	lt7r@nih.gov
Scientific Review Program (SRP)				
Hortencia M. Hornbeak, Ph.D., *Director*	6700B	2101	(301) 496-2550	hh7q@nih.gov
AIDS Clinical and Epidemiology Research Review Branch (ACERRB)				
Peter R. Jackson, Ph.D., *Chief*	6700B	2154	(301) 496-2550	pj8v@nih.gov
AIDS Preclinical Research Review Branch (APRRB)				
Dianne E. Tingley, Ph.D., *Chief*	6700B	2148	(301) 496-2550	dt15g@nih.gov
Microbiology and Immunology Review Branch (MIRB)				
Edward Schroder, Ph.D., *Chief*	6700B	2156	(301) 496-2550	es170m@nih.gov
Special Review Branch (SRB)				
Madelon C. Halula, Ph.D., *Chief*	6700B	2150	(301) 496-2550	mh30x@nih.gov
DIVISION OF INTRAMURAL RESEARCH (DIR)				
Thomas J. Kindt, Ph.D., *Director*	10	4A31	(301) 496-3006	tk9c@nih.gov
Karyl S. Barron, M.D., *Deputy Director*	10	4A30	(301) 402-2208	kb18p@nih.gov
H. Clifford Lane, M.D., *Clinical Director*	10	11B09	(301) 496-7196	cl17d@nih.gov
Linda Coe, R.N., *Associate Clinical Director*	10	11C442	(301) 402-1420	lc89m@nih.gov
Marshall Bloom, *Associate Director for Rocky Mountain Laboratory*	RML		(406) 363-9275	mbloom@niaid.nih.gov
W. Randy Elkins, D.V.M., *Associate Director for Nonhuman Primate Research*	TWNII	201D	(301) 496-0560	re9k@nih.gov
Wendy J. Fibison, Ph.D., *Associate Director for Special Emphasis Programs*	15B-1	103	(301) 496-6400	wf15c@nih.gov
Robert Hohman, Ph.D., *Associate Director for Development of Research Technologies*	TWNI	1004	(301) 594-8198	rh13q@nih.gov
Animal Care Branch (ACB)				
W. Randy Elkins, D.V.M., *Acting Chief*	TWNII	201D	(301) 496-0560	re9k@nih.gov
Infectious Disease Pathogenesis Branch (IDPB)				
W. Randy Elkins, D.V.M., *Chief*	TWNII	201D	(301) 496-0560	re9k@nih.gov
Research Technologies Branch (RTB)				
Robert Hohman, Ph.D., *Chief*	TWNI	1004	(301) 594-8198	rh13q@nih.gov
Laboratory of Allergic Diseases (LAD)				
Dean D. Metcalfe, M.D., *Chief*	10	11C205	(301) 496-1267	dm15o@nih.gov
Laboratory of Cellular and Molecular Immunology (LCMI)				
Ronald H. Schwartz, M.D., Ph.D., *Chief*	4	111	(301) 496-8108	rs34r@nih.gov
Laboratory of Clinical Investigation (LCI)				
Stephen E. Straus, M.D., *Chief*	10	11N228	(301) 496-5807	ss44z@nih.gov
Warren Strober, M.D., *Deputy Chief*	10	11N238	(301) 496-6810	ws9j@nih.gov
Laboratory of Host Defenses (LHD)				
John I. Gallin, M.D., *Chief*	10	2C128	(301) 496-1343	jg21z@nih.gov
Harry L. Malech, M.D., *Deputy Chief*	10	11N113	(301) 496-1343	hm5s@nih.gov

	BLDG.	ROOM	PHONE	E-MAIL
Laboratory of Human Bacterial Pathogenesis (LHBP)				
James M. Musser, M.D., *Chief*	RML		(406) 363-9315	jm521n@nih.gov
Laboratory of Immunogenetics (LIG)				
Susan K. Pierce, Ph.D., *Chief*	TWNII	200B	(301) 496-9589	sp217q@nih.gov
Laboratory of Immunology (LI)				
William E. Paul, M.D., *Chief*	10	11N311	(301) 496-5046	wp1k@nih.gov
Ronald N. Germain, M.D., Ph.D., *Deputy Chief*	10	11D14	(301) 496-1904	rg14b@nih.gov
Laboratory of Immunopathology (LIP)				
Herbert C. Morse III, M.D., *Chief*	TWNI	1421	(301) 496-6379	hm16c@nih.gov
Laboratory of Immunoregulation (LIR)				
Anthony S. Fauci, M.D., *Chief*	10	11B13	(301) 496-1124	af10r@nih.gov
Laboratory of Infectious Diseases (LID)				
Brian R. Murphy, M.D., *Acting Cochief*	50	6517	(301) 594-1616	bm25f@nih.gov
Robert Purcell, M.D., *Acting Cochief*	50	6523	(301) 496-6227	rp18p@nih.gov
Laboratory of Intracellular Parasites (LICP)				
Harlan D. Caldwell, Ph.D., *Chief*	RML		(406) 363-9333	hcaldwell@niaid.nih.gov
Laboratory of Molecular Microbiology (LMM)				
Malcolm A. Martin, M.D., *Chief*	4	315	(301) 496-4012	mm54y@nih.gov
Laboratory of Malaria and Vector Research (LMVR)				
Thomas E. Wellems, M.D., Ph.D., *Acting Chief*	4	126	(301) 402-1274	tw4i@nih.gov
Laboratory of Parasitic Diseases (LPD)				
F. Alan Sher, Ph.D., *Acting Chief*	4	126	(301) 496-4882	as28c@nih.gov
Laboratory of Persistent Viral Diseases (LPVD)				
Bruce W. Chesebro, M.D., *Chief*	RML		(406) 363-9354	bchesebro@nih.gov
Laboratory of Viral Diseases (LVD)				
Bernard Moss, M.D., Ph.D., *Chief*	4	229A	(301) 496-9421	bm26f@nih.gov
Rocky Mountain Laboratory Microscopy Branch (RMMB)				
Claude F. Garon, Ph.D., *Chief*	RML		(406) 363-9228	cg1t@nih.gov
Rocky Mountain Veterinary Branch (RMVB)				
Michael J. Parnell, D.V.M., Ph.D., *Chief*	RML		(406) 363-9238	mp24s@nih.gov

[a] Current as of December 9, 2002. For locating personnel not listed, the telephone number for general NIH information is (301) 496-4000. Information is available online at www.niaid.nih.gov/cgi-shl/contacts/contacts.cfm. For direct dialing, the area code is 301, unless otherwise noted.

[b]
6700B —6700B Rockledge Drive, Bethesda, MD 20892
Dmc2 —Office of Management for New Initiatives, 6707 Democracy Boulevard, Suite 880, Bethesda, MD 20892
FCRDC —Frederick Cancer Research and Development Center, Building 550, Ft. Detrick, MD 21702
RML —Rocky Mountain Laboratories, 903 South Fourth Street, Hamilton, MT 59840-2999
TWNI —Twinbrook I Building, 5640 Fishers Lane, Rockville, MD 20857
TWNII —Twinbrook II Building, 12441 Parklawn Drive, Rockville, MD 20857
Building 4 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 7 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 10 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 14B-S —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 15B-1 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 31 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 40/VRC —Dale and Betty Bumpers Vaccine Research Center, NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 50 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892

Location of Buildings Occupied by NIAID Personnel



a Building 4
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

b Building 10
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

c Building 14B-S
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

d Building 15B-1
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

e Building 31
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

f Building 40/VRC
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

g Building 50
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

h Democracy 2
6707 Democracy Boulevard
Suite 880
Bethesda, MD 20892

i Fernwood Building
10401 Fernwood Road
Bethesda, MD 20892

j Frederick Cancer Research and Development Center
Building 550
Ft. Detrick, MD 21702

k Rockledge Building (6700A)
6700 A Rockledge Drive
Bethesda, MD 20892

l Rockledge Building (6700B)
6700 B Rockledge Drive
Bethesda, MD 20892

m Rockledge Building (6610)
6610 Rockledge Drive
Bethesda, MD 20892

n Rocky Mountain Laboratories
903 South Fourth Street
Hamilton, MT 59840

o Twinbrook Building #1
5640 Fishers Lane
Rockville, MD 20857

p Twinbrook Building #2
12441 Parklawn Drive
Rockville, MD 20857